Drug Development & Delivery

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AI in Drug Discovery

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

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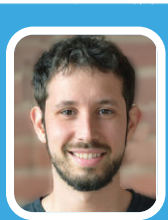

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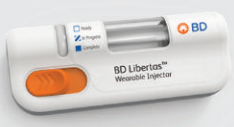

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AI in Drug Discovery

"Artificial intelligence is attracting significant attention and investment for drug discovery. At least 97 relevant start-ups and 28 pharmaceutical companies use AI in some way. But not all applications are equal. Companies that combine domain expertise, deep learning, and proprietary data stand apart."

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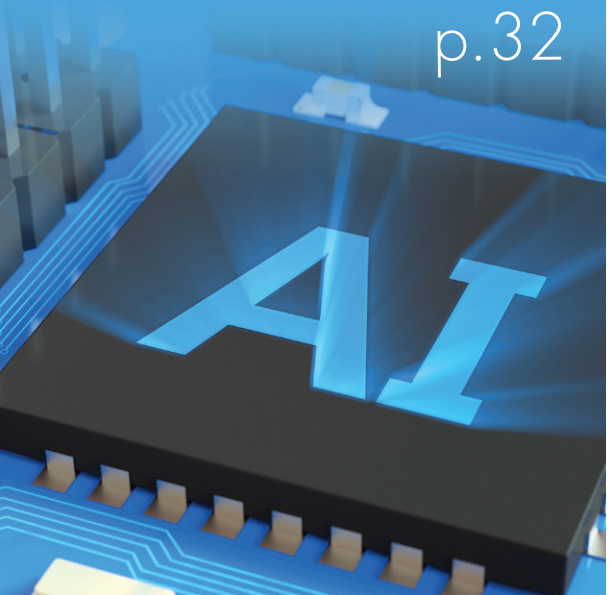

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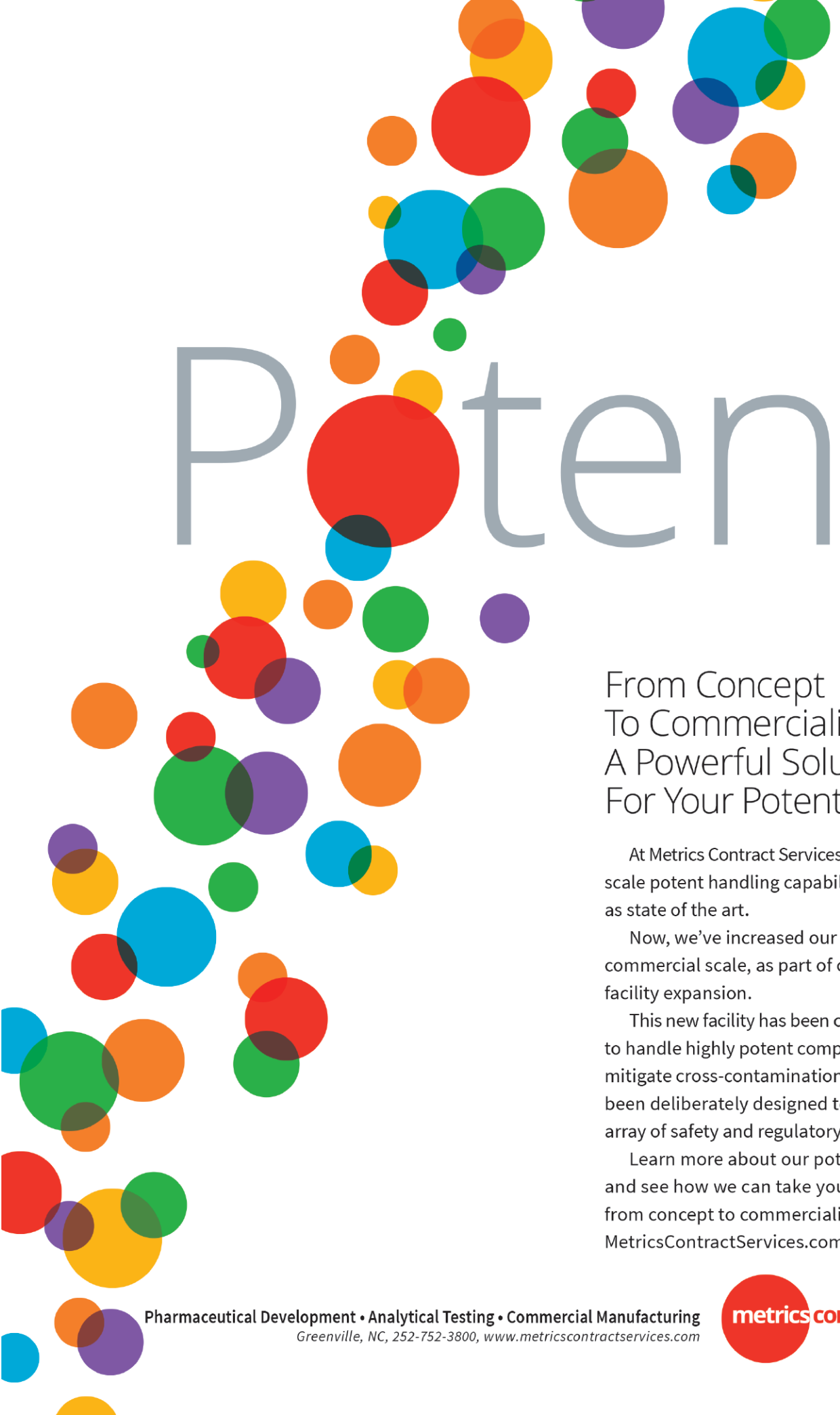

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"Like all drug delivery devices, a successful WI must be designed to meet the needs of a variety of healthcare stakeholders. Most importantly, the WI must meet patients' needs for simplicity in the non-clinical setting. However, WIs must also meet the pharmaceutical manufacturer's needs for a solution that offers proven, well-integrated components that fit into existing fill/finish processes."

p.48

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ContraVir Pharmaceuticals Announces Completion of Phase 1 With CRV431

ContraVir Pharmaceuticals, Inc. recently announced that the primary endpoints of safety and tolerability were met in a single ascending dose (SAD) study of CRV431 conducted in the United States.

Subjects in the study were treated with escalating doses of CRV431 administered as a single dose. In addition to a favorable safety and tolerability profile, pharmacokinetic (PK) profiling demonstrated CRV431 exposure levels that are anticipated to be efficacious in future HBV patient studies.

"We are extremely pleased with the PK results in this study indicating good exposure to CRV431," said James Sapirstein, Chief Executive Officer of ContraVir. "The positive results from this trial support the continued development of CRV431 in a Phase 2 clinical efficacy study. Continued progress of our CRV431 clinical program allows ContraVir to drive toward its goal of participating in a curative regimen for Hepatitis B in a streamlined development program as announced earlier this year."

As a first-in-class host targeting candidate medicine, CRV431 is expected to complement other anti-HBV viral agents. CRV431 is a non-immunosuppressive analog of cyclosporine A (CsA) whose primary biochemical action is inhibition of cyclophilin isomerase activity, playing a key role in protein folding. Other viruses such as HIV-1 and HCV, similarly use cyclophilin for their replication. In pre-clinical studies, CRV431 has shown potential in experimental models to complement current hepatitis B treatments by reducing multiple markers of infection including HBV DNA, HBsAg, HBx, HBeAg, and HBV uptake by cells. Studies have also demonstrated that CRV431 reduces the progression of fibrosis in an animal model and also reduces both the number and size of liver tumors in a hepatocellular carcinoma (HCC) model.

ContraVir is a biopharmaceutical company focused on the development and commercialization of targeted antiviral therapies with a specific focus on developing a potentially curative oral therapy for hepatitis B virus (HBV). The company is developing two novel anti-HBV compounds with complementary mechanisms of action. TXL, a direct acting antiviral (DAA) nucleotide analog lipid prodrug of tenofovir (TFV), is designed to deliver higher hepatic intracellular concentrations of the active tenofovir species (tenofovir diphosphate) while reducing concentrations of tenofovir outside the liver, causing fewer off-target toxicities and side-effects. CRV431, the other anti-HBV compound, is a host-targeting antiviral (HTA) next-generation cyclophilin inhibitor with a novel chemical structure that optimizes the selective index against HBV. In vitro and in vivo studies have thus far demonstrated that CRV431 reduces HBV DNA and other viral proteins, including surface antigen (HBsAg), while offering additional benefits to mitigate liver disease. For more information, visit www.contravir.com.

ProMach Acquires FLtecnics, Leading Manufacturer of Horizontal-Form-Fill Seal Pouch Packaging Solutions

ProMach continues to expand its global footprint and flexible packaging product line with the acquisition of FLtècnics of Girona, Spain. ProMach's relationship with the European horizontal form-fill-seal pouch provider began in 2014 when it began to sell and support FLtècnics products in the North American market.

"Five years ago, we saw a growing need in the North American marketplace for a single source provider of a full range of flexible packaging solutions," said Mark Anderson, ProMach President and CEO. "We have invested in this space through product development, acquisitions, and strategic partnerships with companies like FLtècnics. They are a technology leader in the horizontal form-fill-seal pouch space and we are excited to invest in their continued product development to bring new innovations and new technology into the global marketplace."

ProMach's Flexibles business line provides a wide variety of flexible packaging machinery solutions, including bags, pouches, sachets, stickpacks, and more from numerous product brands for a wide range of industries. In recent years ProMach has increased its focus on markets outside North America, particularly the Latin American and European marketplace, resulting in double-digit annual growth of international sales. The addition of FLtècnics helps ProMach strengthen its global position in the fast-growing stand-up pouch market.

"Over the past 5 years the flexible packaging market has continued expanding not just in North America, but all over the world," says Mr. Anderson. "The global stand-up pouch market, in particular, is showing highly favorable tailwinds for continued strong growth over the next 5 years, which makes taking the next step to bring FLtècnics fully into the ProMach family of product brands a natural fit."

FLtècnics manufactures innovative servo-controlled carrousel and walking-beam horizontal form-fill-seal machines capable of packaging 400 pouches per minute for the food, liquid, cosmetics, chemical, and pharmaceutical industries. Formats include flat pouches, stand up pouches, spouted pouches, zipper pouches, Velcro pouches, three side seal pouches, and more.

FLtècnics leadership, sales, engineering, and customer service staff are joining the ProMach Flexibles team. Current FLtècnics CEO Mateo Lara and COO Pablo Pizarro will continue leading the product brand as Vice President & General Manager and Vice President of Operations, respectively.

"ProMach and FLtècnics have demonstrated tremendous success working together these past four years," says Mr. Lara. "This will be a seamless transition for our team and our customers and we look forward to introducing ProMach solutions more deeply into the marketplace."

"We're enthusiastic about this opportunity to expand our sales and service further into the global market," adds Mr. Anderson. "Our customers receive best-in-class solutions for their unique environments and ProMach can also provide integrated turnkey systems upstream and downstream of the pouch machines for complete packaging lines."

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Inovio Develops Novel H3N2 Influenza DNA Vaccine; Generates Cross-Reactive Responses & Provides Complete Protection Against Lethal Preclinical Challenges

Inovio Pharmaceuticals, Inc. recently announced its SynCon vaccine approach using a collection of DNA antigens generated broadly protective antibody responses against the most deadly strains of the H3N2 influenza viruses from the past 50 years and provided complete protection against heterologous lethal challenge in a preclinical study.

Study results were published online in the journal, Human Gene Therapy, in an article by Inovio and its collaborators entitled, A Synthetic Micro-Consensus DNA Vaccine Generates Comprehensive Influenza-A H3N2 Immunity and Protects Mice Against Lethal Challenge by Multiple H3N2 Viruses. This work was supported by a grant from the US National Institutes of Health. Inovio is currently in discussions with third-party funders to support further development of the company's technology with its advantages in promoting global human health.

Throughout the 2017-18 flu season the commercially available H3N2 vaccine efficacy was reported low due to the mismatch between the vaccine and circulating H3N2 viruses. In some populations the vaccine showed only 13% effectiveness, which contributed to a much greater rate of pneumonia and flu-related deaths. In a pursuit of overcoming the antigenic diversity of H3N2 viruses, Inovio developed a collection of H3HA DNA antigens and demonstrated broad, functional antibody responses against H3 viruses in mice. Vaccination was also capable of inducing robust CD4 and CD8 T cell responses, which are reported to be critical for prevention of disease in the elderly population. Additionally, all (100%) vaccinated mice survived when infected with 10 times of the lethal viral doses from two of the H3N2 virus which circulated during the 1968 and 1982 outbreaks, highlighting the strong protection afforded by Inovio's H3HA vaccine.

Dr. Laurent Humeau, Inovio's Senior Vice President, Research & Development, said "This study is a step towards conquering the diversity of the H3N2 flu viruses that has vexed researchers for years. In this preclinical study, Inovio demonstrated that its SynCon method of antigen design is capable of providing protection against multiple H3N2 strains."

Earlier this year Inovio reported that its synthetic vaccine approach using a collection of synthetic DNA antigens generated broad protective antibody responses against all major deadly strains of H1 influenza viruses from the last 100 years including the virus that caused "Spanish Flu" in 1918 in multiple animal models including mice, guinea pigs and non-human primates. According to CDC, H3N2 hits people harder than other seasonal flu strains and can be especially deadly among vulnerable groups like the elderly and children. Researchers still aren't sure why, but they've found that a flu season involving the H3 virus is generally more virulent — with more hospitalizations and flu-related deaths — than seasons involving mostly H1N1 or influenza B viruses. Furthermore, the H3 part of the commercially available vaccine doesn't just work poorly in older adults. Last year adults aged 18 to 49 got very little protection—13%—from the H3 component.

Thermo Fisher Scientific to Launch Global Customer Solution Centers

Thermo Fisher Scientific Inc. recently announced its intent to open multiple Global Customer Solution Centers. The new Global Customer Solution Centers will focus on meeting and exceeding the demands of scientists in food, beverage, pharmaceutical and biotech laboratories by developing critical workflows and integrated solutions that help advance chromatography and mass spectrometry worldwide.

With the scientific community determined to overcome key challenges such as global food security and the need to develop novel therapeutics faster, each Customer Solution Center will serve as a unique hub for scientists, customers and regulatory bodies to collaborate with Thermo Fisher subject matter experts. By bringing together leading minds and instrumentation, the network of sites will focus on training, support and the development of next-generation workflows and integrated solutions designed to increase productivity, ease-of-use and return on investment for customers.

"The announcement of the Global Customer Solution Centers demonstrates our commitment to helping scientists push research and technology to the next level," said Jakob Gudbrand, President, Chromatography and Mass Spectrometry, Thermo Fisher Scientific. "Our network of sites will create hubs around the globe for scientists, collaborating organizations and regulatory bodies to work together and develop workflows that will make the world healthier, cleaner and safer."

"Our research team is confronted with real-life problems within the biopharmaceutical industry every day," said Christian Huber, Professor and Head of the Christian Doppler Laboratory for Innovative Tools for Biosimilar Characterization at the University of Salzburg, Austria. "The analytical tools we develop have significant potential of eventually being implemented in routine analytical workflows for quality control. Our cooperation with the new Thermo Fisher Bio/Pharma Customer Solution Centers offers the possibility of employing the latest workflows for molecular characterization based on cutting-edge high-performance liquid chromatography and mass spectrometry."

"In India, the Food Safety and Standards Authority of India (FSSAI) establishes science-based standards for articles of food and regulates their manufacture, storage, distribution, sale and import to ensure availability of safe and wholesome food to the country's 1.3 billion citizens," said Pawan Agarwal, Chief Executive Officer, FSSAI.

"The collaboration between the FSSAI and Thermo Fisher at the Food Safety Customer Solution Center in Delhi will help us build new workflows for food safety testing, train our food centers of excellence and help build capacity and expertise in the region," said Bhaskar Narayan, PhD, Advisor of Quality Assurance, FSSAI.

The inaugural phase of this new global strategic initiative will be marked by multiple Customer Solution Center openings in locations across the world including India and China, followed by additional centers in the U.S. and Europe. Thermo Fisher Scientific Inc. is the world leader in serving science, with revenues of more than $20 billion and approximately 70,000 employees globally. Our mission is to enable our customers to make the world healthier, cleaner and safer.

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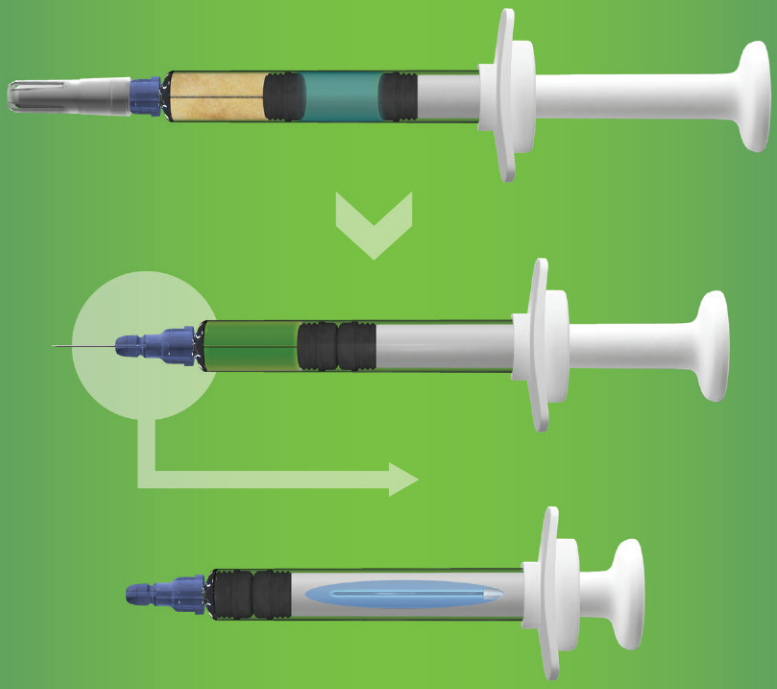

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Molecular Templates Announces Agreement With Takeda for Joint Development of Protein-Based Oncology Therapy

Molecular Templates, Inc. recently announced an agreement with Takeda Pharmaceutical Company Limited for the joint development of CD38-targeted engineered toxin bodies (ETBs) for the treatment of patients with diseases such as multiple myeloma. The lead development candidate is a CD38-targeted ETB that resulted from a previous discovery collaboration between the two companies.

The parties developed preclinical stage ETBs targeting CD38 under the prior discovery collaboration. Takeda and Molecular Templates will further develop the ETBs for the treatment of multiple myeloma under this new license, development and commercialization agreement.

"This collaboration builds on Takeda's deep history and commitment to the study of blood cancers, including multiple myeloma," said Philip Rowlands, PhD, Head, Oncology Therapeutic Area Unit at Takeda. "Throughout our research collaboration with Molecular Templates, we have seen the promise of its ETB platform for the discovery and development of new therapies. As we expand our relationship and continue to explore next-generation modalities, our hope is to bring forth new and important treatment options for patients."

Under the terms of the agreement, Takeda will make an upfront payment of $30 million and Molecular Templates is eligible to receive development, regulatory, and commercial milestone payments of up to $632.5 million if Molecular Templates exercises its co-development option or $337.5 million if Molecular Templates does not exercise or opts out of its co-development option. Takeda has also agreed to pay royalties on sales of the commercial product developed through the collaboration. Molecular Templates and Takeda will share equally in the development costs.

"We have worked closely with Takeda's scientific team since October 2016 to develop CD38-targeted ETBs with substantial improvements over our own internal program, MT-4019," said Eric Poma, PhD, Molecular Templates' Chief Executive and Scientific Officer. "Takeda's expertise in multiple myeloma and strong antibody capabilities allowed us to develop CD38-targeted ETBs that, of the ones tested to date, are the most potent ETBs we have created with our platform. We look forward to moving this program into the clinic."

Multiple myeloma cells widely express the CD38 protein, making it an increasingly important target in the development of therapeutics for multiple myeloma. CD38-targeted ETBs recognize the protein and deliver a modified bacterial toxin that enters the myeloma cells and destroys them through the enzymatic and irreversible destruction of ribosomes. Unlike other CD38-targeted therapies, ETBs are not reliant on the body's own immune system for effectiveness, offering the potential of broader and deeper responses.

Molecular Templates is focused on the discovery, development and commercialization of next-generation immunotoxins called Engineered Toxin Bodies (ETBs) for the treatment of cancers and other serious diseases. For more information, visit www.mtem.com.

Evonik Completes Multi-Million Dollar Expansion of its CMO Capabilities for API & Advanced Intermediates

Evonik, a global CMO leader for API and advanced intermediates, recently announced the completion of a 36-million euro expansion of its contract manufacturing capabilities in the US and Europe. A series of advanced technologies, including high-potency API (HPAPI), fermentation, mPEGs, and continuous processing, have been introduced or enhanced at multiple Evonik production sites throughout the past year.

"Our mission is to help our customers bring to market innovative molecules with complex manufacturing processes, and in this context, global scale, expertise and flexibility matter," said Dr Jean-Luc Herbeaux, SVP and Head of the Evonik Health Care business line. "Evonik will continue to be a leader in advanced technologies that make the industrialization and commercialization of these highly specialized products possible."

At its facility in Hanau, Germany, Evonik has recently commissioned a new modular cGMP continuous processing plant, a pilot plant for the custom synthesis of highly pure PEGs and mPEGs for pharmaceutical applications, as well as a cGMP suite for the small-scale production of HPAPI and ultra-HPAPI.

At its facilities in Tippecanoe, IN, and Hanau, Germany, Evonik has increased its asset footprint and added additional capacities to support the small, medium or large scale production of HPAPI. In addition to being the world's largest HPAPI manufacturer, Evonik is now able to run several HPAPI projects in parallel down to an exposure level (OEL) of 5ng/m^3.

At its facility in Slovakia, Evonik has recently invested in a new, flexible pilot plant for downstream processing. It is the sixth plant in a worldwide network to support microbial fermentation projects from strain development through to commercial manufacturing.

Dr Andreas Meudt, VP and Head of Exclusive Synthesis at Evonik, said "Advanced technologies will continue to be deployed across our global network in response to emerging customer needs. In parallel, our commitment to quality and regulatory excellence will continue to drive all business activities. The fact that our Tippecanoe facility in the U.S. has now recorded six consecutive FDA inspections without a Form 483 is an indication of how we can provide customers with peace-of-mind."

Evonik is one of the world leaders in specialty chemicals. The focus on more specialty businesses, customer-orientated innovative prowess and a trustful and performance-oriented corporate culture form the heart of Evonik's corporate strategy. They are the lever for profitable growth and a sustained increase in the value of the company. Evonik benefits specifically from its customer proximity and leading market positions. Evonik is active in over 100 countries around the world with more than 36,000 employees. In fiscal 2017, the enterprise generated sales of 14.4 billion euros and an operating profit (adjusted EBITDA) of 2.36 billion euros

Beta Bionics Secures $50-Million Financing for Bionic Pancreas

Beta Bionics, Inc. recently announced it has so far raised $50 million of a Series B equity financing. The round was led by Eventide Asset Management, LLC, the advisor to Eventide Mutual Funds. Eventide was founded in 2008 with a vision to provide high performance, value-based investments that are socially responsible. RTW Investments, LP also participated, along with Series A investor, Novo Nordisk A/S. Strategic partner Zealand Pharma A/S, developer of a stable and pump compatible glucagon analog, called dasiglucagon, previously committed $5 million to the round. Funds will be used to support ongoing product development of the Beta Bionics' commercial-generation bionic pancreas technology for use in its insulin-only, glucagon-only, and bihormonal configurations.

Beta Bionics is developer of the iLet Bionic Pancreas System, which is currently deployed in home-use clinical trials in adults and children with type 1 diabetes (T1D), as previously announced in May and July 2018. The iLet consists of a dual-chamber, autonomous, infusion system that mimics a biological pancreas. Embedded in the system are clinically tested mathematical dosing algorithms driven by lifelong machine learning to autonomously calculate and dose insulin and/or glucagon as needed, based on data from a continuous glucose monitor. Designed with simplicity of use, the iLet requires only body weight for initialization and then proceeds to autonomously control the individual's blood-glucose levels, and to continuously adapt to the individual's ever-changing insulin needs.

The iLet bionic pancreas system is a pocket-sized, wearable medical device that autonomously controls blood-sugar levels in people with diabetes. The mathematical dosing algorithms integrated into the iLet were licensed by Beta Bionics from Boston University and were refined over years of clinical research to incorporate lifelong machine learning technology that adapts continuously to each person's unique insulin requirements. In previous home-use and outpatient studies in adults and children with T1D, these algorithms demonstrated dramatic improvements in glycemic control relative to the standard of care. These improvements included significant reductions in blood-glucose levels, in hypoglycemia, and in intersubject and intrasubject glycemic variability (New England Journal of Medicine. 2014, 371:313-25; Lancet Diabetes and Endocrinology. 2016, 4:233-43; Lancet. 2016, 389:369-80).

The iLet is initialized by entering body weight only and does not require the patient to count carbohydrates, set insulin delivery rates or deliver bolus insulin for meals or corrections. The iLet is effectively three medical devices in one. It can be configured as an insulin-only bionic pancreas, a glucagon-only bionic pancreas, or a dual-hormone bionic pancreas. The glucagon-only configuration may be helpful in rare, chronic, low-blood-sugar conditions, such as congenital hyperinsulinism (CHI) and insulinoma syndrome. Beta Bionics is committed to obtaining regulatory approval and commercializing all three iLet configurations.

Beta Bionics is a for-profit Massachusetts public benefit corporation founded in 2015 to commercialize the iLet, a revolutionary bionic pancreas that is driven by mathematical dosing algorithms to autonomously control glycemia in people with diabetes.

VistaGen Therapeutics Acquires Worldwide License of Phase 3-Ready CNS Drug Candidate

VistaGen Therapeutics, Inc. and Pherin Pharmaceuticals, Inc. recently announced the signing of a license agreement granting VistaGen exclusive worldwide rights to develop and commercialize PH94B nasal spray, a Phase 3-ready drug candidate for as-needed (PRN) treatment of Social Anxiety Disorder (SAD).

Pherin's first-in-class proprietary compounds called "pherines" are synthetic neuroactive steroids that engage nasal chemosensory receptors which, in turn, inhibit nerve circuits mediating behavioral and physiological effects of anxiety. This mechanism of action, the rapid onset of efficacy, and the excellent safety and tolerability profile shown in multiple previous clinical trials, including a pilot Phase 3 feasibility study for evaluating the safety and efficacy of PH94B, make PH94B a novel product candidate for the acute, intermittent and long-term treatment of individuals with SAD.

An estimated 12.1% of US adults experience SAD at some time in their lives. SAD is characterized by excessive anxiety about scrutiny or evaluation by others that leads an individual to avoid social situations and/or performance.2 SAD affects social, academic and work life, and often presents with other anxiety disorders, MDD and substance use disorders, and the onset of SAD generally precedes that of other disorders.3 Currently, selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are FDA-approved for treatment of SAD, but they take weeks to months to work, must be taken chronically and present numerous side effects.

VistaGen has also acquired an option from Pherin to license an additional CNS neuropsychiatry-focused product in Phase 2 development. In connection with the consummation of the license and option agreements, VistaGen issued to Pherin $2.25 million of unregistered common stock (1,630,435 unregistered shares).

PH94B was developed from proprietary compounds called pherines. Administered as a nasal spray, PH94B acts locally on peripheral nasal chemosensory receptors that trigger rapid activation of the limbic system areas of the brain associated with SAD. This mechanism of pharmacological action, the rapid onset of efficacy, and the excellent safety and tolerability profile shown in clinical trials make PH94B an excellent product candidate for the acute intermittent and long-term treatment of individuals with SAD.

AV-101 is an oral, non-opioid, non-sedating NMDA receptor glycine B antagonist with potential to be a new at-home treatment for major depressive disorder and multiple CNS indications with high unmet need. AV-101 is currently in Phase 2 clinical development in the United States. ELEVATE is VistaGen's ongoing Phase 2 clinical trial designed to evaluate the efficacy and safety of adjunctive use of oral AV-101 for MDD in individuals with an inadequate response to standard antidepressant therapy with either an FDA-approved SSRI or SNRI. The FDA has granted Fast Track designation to AV-101 for development as a potential adjunctive treatment of MDD.

Biothera Pharmaceuticals Announces Immuno-Oncology Clinical Trial Collaboration With AstraZeneca

Biothera Pharmaceuticals, Inc. recently announced a clinical collaboration with AstraZeneca to evaluate whether the combination of Biothera's Imprime PGG and AstraZeneca's durvalumab (IMFINZI) can decrease tumor volume in patients with primary untreated locally advanced head and neck cancer prior to surgical resection. Imprime PGG is an innate immune trigger that activates anti-cancer T cells. Durvalumab is a human monocolonal antibody that blocks the immune checkpoint protein, programmed death-ligand (PD-L1), and allows activated T cells to attack tumor cells.

Under terms of the agreement, Biothera and AstraZeneca will collaborate on a non-exclusive basis to evaluate the combination of the two drugs in head and neck squamous cell carcinoma, in the neoadjuvant setting. Biothera expects to initiate the randomized Phase 2 study in the second half of 2018. Biothera will sponsor and fund the study, and AstraZeneca will supply durvalumab for the study. The trial will be conducted at several clinical sites, including Sanford Health, one of the largest nonprofit healthcare systems in the US. Completion of patient enrollment is expected in 2019.

"We are pleased to work with AstraZeneca in hopes of addressing the high unmet clinical needs of patients with head and neck cancer," said Barry Labinger, Biothera Pharmaceuticals' President and Chief Executive Officer. "Previous clinical and preclinical studies demonstrated that Imprime PGG consistently repolarized the immunosuppressive tumor microenvironment and increased T cell infiltration and activation, which we believe will have a synergistic effect with durvalumab's targeting of PD-L1."

Durvalumab, a human monoclonal antibody directed against PD-L1, blocks PD-L1 interaction with PD-1 and CD80 on T cells, countering the tumor's immune-evading tactics and inducing an immune response. As part of a broad development program, durvalumab is being investigated as monotherapy and in combination with immune-oncology, small molecules, and chemotherapies across a range of tumors and stages of disease.

Imprime PGG is a Phase 2 cancer immunotherapy that has been shown in preclinical studies to enhance the efficacy of anti-cancer immune responses in combination with immune checkpoint inhibitor, tumor-targeting and anti-angiogenic antibodies.

Biothera Pharmaceuticals is a privately held clinical stage immuno-oncology company developing Imprime PGG. In addition to its collaboration with AstraZeneca, the company has clinical research agreements with Merck to evaluate Imprime PGG and KEYTRUDA (pembrolizumab), Merck's anti-PD-1 therapy, in Phase 2 studies in advanced melanoma, metastatic triple negative breast cancer and head and neck squamous cell cancer; Genentech to study Imprime PGG in combination with TECENTRIQ (atezolizumab) and AVASTIN (bevacizumab) in metastatic colorectal cancer; and The Big Ten Cancer Research Consortium, which is evaluating Imprime PGG and KEYTRUDA in a Phase 1b/2 trial in patients with non-small cell lung cancer.

IMV Announces Phase 2 Basket Trial in Collaboration With Merck

IMV Inc. recently announced it has expanded its clinical program with a Phase 2 basket trial evaluating its lead candidate, DPX-Survivac, in combination with low- dose cyclophosphamide and Merck's anti-PD-1 therapy, KEYTRUDA (pembrolizumab) in patients with select advanced or recurrent solid tumors.

"The clinical data from our recent ASCO meeting presentation demonstrated for the first time the unique potential of DPX-Survivac to generate solid tumor regressions in ovarian cancer," said Frederic Ors, Chief Executive Officer, IMV Inc. "We are delighted to expand our clinical program and collaboration with Merck across multiple cancer indications, and look forward to investigating the potential added benefit of combining DPX-Survivac and KEYTRUDA."

The open-label, multicenter, Phase 2 basket study will evaluate the safety and efficacy of the immunotherapeutic combination agents in patients with bladder, liver (hepatocellular carcinoma), ovarian, or non-small cell lung (NSCLC) cancers as well as tumors shown to be positive for the microsatellite instability high (MSI-H) biomarker. Investigators plan to enroll more than 200 patients across five indications at multiple medical centers in Canada and the US. IMV expects to initiate trial enrollment in the 4th quarter of 2018.

The American Society of Clinical Oncology (ASCO) defines a basket clinical study as a trial that investigates the effects of a drug regimen in multiple tumor types that share a common molecular target, regardless of where the disease originated.

This is the third clinical trial evaluating the combination of DPX-Survivac, low- dose cyclophosphamide, and pembrolizumab in advanced recurrent cancers. Two ongoing investigator-sponsored Phase 2 trials are evaluating this combination in patients with advanced ovarian cancer and diffuse large B-cell lymphoma (DLBCL).

DPX-Survivac is the lead candidate in IMV's new class of immunotherapies that programs targeted T cells in vivo. It has demonstrated the potential for industry-leading targeted, persistent, and durable T cell activation against cancer. IMV believes this MOA is key to generating durable regressions in solid tumors. DPX-Survivac consists of survivin-based peptide antigens formulated in IMV's proprietary DPX drug delivery platform. DPX-Survivac is believed to work by eliciting a prolonged cytotoxic T cell attack on cancer cells presenting survivin peptides.

Survivin, recognized by the National Cancer Institute (NCI) as a promising tumor-associated antigen, is broadly over-expressed in most cancer types, and plays an essential role in antagonizing cell death, supporting tumor-associated angiogenesis, and promoting resistance to anti-cancer therapies. IMV has identified over 15 cancer indications in which the over-expression of survivin can be targeted by DPX-Survivac.

DPX-Survivac has received Fast Track designation from the US FDA as maintenance therapy in advanced ovarian cancer, as well as orphan drug designation status from the US FDA and the European Medicines Agency (EMA) in the ovarian cancer indication. It is currently being evaluated in multiple Phase 1b/2 clinical trials.

Telix Completes Acquisition of Atlab for Prostate Cancer Program

Telix Pharmaceuticals Limited recently announced completion of the acquisition of Atlab Pharma SAS. The option to acquire Atlab for the consideration of $10 million (in cash or shares, at Telix's election) was previously disclosed in Telix's IPO prospectus. As part of the acquisition, Telix has renegotiated Atlab's material background intellectual property licenses, notably with BZL Biologics LLC. BZL is the holder of a portfolio of patents originating from Professor Neil Bander's laboratory at Weill Cornell Medical Centre (WCMC, NY).

PSMA is a cell surface antigen that is has relatively little expression in normal tissues and represents a validated and highly promising target for a range of therapeutic strategies, particularly radiopharmaceuticals. PSMA expression has been detected in a limited range of normal tissues, including benign prostatic epithelium, renal proximal tubules, small bowel, and the brain (a subset of astrocytes). However, these tissues generally express PSMA at levels 2 to 3 orders of magnitude lower than that observed in prostate cancer.

Antibody-directed cytotoxicity (whether via targeted radiation or other therapeutic strategies) offers several advantages over small molecule or peptide-based delivery approaches. Normal tissues that express PSMA are highly polarized to the apical/luminal aspect of the benign prostatic glands, renal tubules, and small bowel, basement membrane and epithelial tight junctions, and therefore form substantial barriers to circulating antibodies. PSMA expression by astrocytes is similarly sequestered behind the blood-brain barrier. Consequently, antibodies to PSMA are functionally tumor-specific, whereas small molecule PSMA ligands excreted via the renal tubular lumen are not. As a result, small molecule and peptide therapies targeting PSMA have shown significant off-target effects not seen with antibodies, which may limit their utility outside of the salvage ("end of life") patient population.

The huJ591 (humanized) mAb is the most clinically-advanced anti-PSMA antibody, with experience in several hundred patients for imaging and therapy, both as a "naked" antibody and with a wide range of diagnostic and therapeutic payloads. Almost 200 patients have been treated with 177Lu-huJ591 at different dosing levels and in combination with other standard care therapies, including androgen deprivation therapy in the metastatic castrate-resistant prostate cancer (mCRPC) setting. In over a dozen clinical trials, huJ591 has demonstrated excellent immunogenicity, safety, tolerability and efficacy, including with repeat dosing.

TLX591 is a "best-in-class" anti-PSMA radiopharmaceutical based on a re-engineered and optimized form of the huJ591 antibody. Telix has engineered the biological properties and production characteristics of huJ591 to deliver enhanced clinical performance and lower manufacturing cost. TLX591 combines the superior therapeutic efficacy of antibody-based pharmaceuticals with the hematologic toxicity profile of rapidly-clearing small molecules targeting PSMA. TLX591, like huJ591, does not target normal tissue PSMA expression or demonstrate the typical exocrine gland uptake that may limit the utility of small molecule PSMA radiopharmaceuticals outside of the salvage (or "end of life") therapy setting.

Christopher R. McCurdy, PhD, FAAPS
2018 President of the American
Association of Pharmaceutical Scientists

Personalized Medicines for Oral Drug Delivery Devices: Definitely NOT Your Father's Tablets

As we near the end of 2018, I'm as excited as I've ever been about new pharmaceutical science technologies on the horizon. Concepts like how to use machine learning and AI technology to truly personalize medicine are starting to become a reality. GSK's ATOM project aims to transform drug discovery and development going from validated target to humans in 1 year or less. When successful, this will revolutionize the pharmaceutical industry.

Another exciting technology that has the potential to create a paradigm shift in the pharmaceutical sciences is 3D printing. The incorporation of 3D printing technology was made a reality with the approval of the first 3D-printed pharmaceutical, Aprecia, by the FDA in 2015. This increased the research and interest around 3D-printed formulations and now, highly sophisticated tablets are being developed with the ability to combine multiple drugs with separate release profiles in a single formulation. The potential for true personalized medicine is within close reach. These are definitely NOT your father's tablets…

Using 3D printing technology, tablets can be created with a simple structure to address some clinical/formulation needs or sophisticated structures, such as compartments with various geometric shapes to modulate the release rate, mode, and onset time.

3D-printed tablets have been created using powder binding (as exemplified by Aprecia) or fused deposition modeling (FDM) 3D-printing technologies for manufacturing or personalized medicine. Using powder binding 3D printing technology, tablets are created with a highly porous structure for fast disintegration. In contrast, using FDM technology, Triastek has fabricated tablets that provide unique pharmacokinetic (PK) profiles for controlling the release rate (zero order or variable kinetics), release mode (pulsatile, immediately or constant release), and onset time. The incorporation of multiple APIs with multiple PK profiles really opens the door for personalized medicines.

Application of FDM 3D printing technology will also revolutionize the formulation development process. Using the processing parameters of excipients and the precision manufacturing of tablets by 3D printing, the release profiles of tablet can be predetermined. Therefore, the tablet can be designed to generate specific release profile to meet clinical needs. A "formulation-by-design" approach has been realized by Triastek using FDM 3D printing technology, which allows the formulation process moving away from traditional formulation by trial method. The formulation-by-design approach gives preclinical and clinical trial formulation a predictable and accelerated development time.

- 3D printing in pharmaceutical tablet application is a new direction for the tablet manufacturing that has been used for more than 150 years.
- FDM 3D printing is capable of fabricating unique architecture within a tablet.
- Formulation-by-design using FDM 3D printing technology represents a paradigm shift in the formulation development of pharmaceutical products.
- 3D printing pharmaceutical manufacturing has its advantage over the traditional tablet manufacturing method but will co-exist with traditional pharmaceutical manufacturing for the foreseeable future.
- 3D printing technology for individualized medicine or personalized medicine has great potential but will not be broadly implemented until regulatory aspects of this technology in place.

In closing, we live in an exciting time in which truly personalized medicine is possible. These advancements in technologies can in turn positively affect patient compliance, patient outcomes, and most importantly, improve global health. ◆

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BUCCAL FILMS

Better Drug Release & Patient Experiences With Buccal Films

By: Robert Davidson and Jessica Rousset

THE BUCCAL REGION – AN ADVANTAGEOUS ROUTE FOR DRUG DELIVERY

Innovations in drug delivery hold the promise of minimizing dose-dependent side effects and maximizing biological activity while improving patient adherence.

Peroral administration of drugs, the preferred route of drug administration in terms of patient experience, has several disadvantages, such as hepatic first-pass metabolism, longer onset of action, and enzymatic degradation of drugs within the gastrointestinal (GI) tract. When GI and hepatic degradation limit a drug's safety or efficacy, invasive injections are often the only viable mode of delivery – with the potential consequence of lower patient adherence.

Buccal administration can achieve local and systemic effects and is attractive in that it overcomes the deficiencies of peroral administration. Indeed, substances absorbed through the buccal mucosa bypass gastrointestinal enzymatic degradation and the hepatic first-pass effect. Buccal administration further represents a better alternative to injections or tablets for those patients who have difficulty swallowing.

What is the Buccal Site?

The buccal area is the inner lining of the cheek and lip, representing about one third of the surface area of the oral cavity (Figure 1).[1] The buccal mucosa consists of a surface layer of stratified squamous epithelium linked to the underlying connective tissue by a basal lamina. A network of blood capillaries is present in the connective tissue where drugs that have permeated through the epithelium can enter the systemic circulation via the internal jugular vein.[2]

The buccal epithelium acts as a barrier to hydrophilic drug permeation, while the connective tissue, which is more hydrophilic in nature, appears to affect the diffusional lag time of lipophilic compounds.[3] Drug transport across the mucosa can be trans- or paracellular (Figure 2), with most hydrophilic drugs and macromolecules permeating through passive paracellular diffusion and lipophilic compounds and small hydrophobic molecules predominantly passing through by paracellular transport.[4] As such, the cell membrane acts as the major transport barrier for hydrophilic compounds, and the intercellular spaces pose as the major barrier to permeation of lipophilic compounds.

The Importance of Mucoadhesion

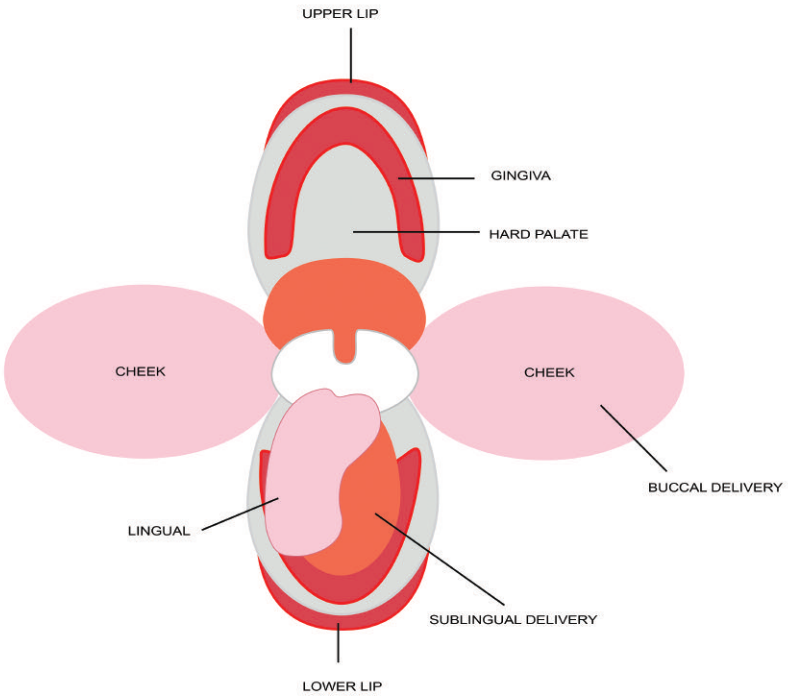
Mucoadhesion is when two surfaces, one of which is a mucous membrane, adhere to each other. It is a critical parameter for buccal administration and formulation materials with optimal adhesive properties to be selected. Mucoadhesion happens in two stages - the contact stage followed by the consolidation stage when adhesive interactions are established. There are likely multiple mechanisms at play causing adhesion. Importantly, adhesive joint failure will occur as a result of overhydration of a dosage form, or as a result of epithelia or mucus turnover. The turnover time for the buccal epithelium has been estimated to be 3 to 8 days compared to about 30 days for the skin.[4]

Site Advantages

In addition to the major benefit of systemic delivery that bypasses liver and gut degradation for greater bioavailability and lesser side effects, the mouth has a relatively large area for drug

application and good accessibility compared to the nose, rectum, and vagina.[5] Also, the rapid cell turnover in the buccal mucosa reduces the risk of tissue damage or irritation.[6] While the sublingual mucosa is more permeable, vascularized and thinner than the buccal mucosa, the surface of this mucosa is smaller, constantly washed by the saliva, and the shear exerted by the tongue makes it difficult to maintain the dosage form in contact with the sublingual mucosa.[7] For all of these reasons, the cheek mucosa is a preferred site within the oral cavity for the administration of controlled-release systems that need to adhere for an extended period of time.[8]

FIGURE 1



Site Limitations

Enhancing the rate of absorbance (μg/mm^2/s) or permeability of the buccal tissue is often necessary to compensate for the limited surface area available. The use of permeation enhancers (ie, substances that reorganize the epidermis or epithelial structures or open up the intercellular tight junctions) is very important in this area. Macromolecules are more complex to deliver through the mucosa due to enzymatic degradation of the saliva and poor permeation across the buccal epithelium without chemical- and electrical-based permeation enhancement.[9] The improper use of permeation enhancers can cause safety concerns as far as local tissue irritation but also as a result of an undesired bolus effect that pushes up the concentration of drug in the blood to levels that are not safe.

An alternative strategy for ensuring higher absorbance of poorly soluble or permeable drugs into the tissue is to increase the dwell time in the mouth. As with permeation enhancers, increasing the dwell time can cause tissue irritation as well as patient discomfort and requires careful evaluation of both immediate and long-term effects on tissue integrity and functionality. Increasing the dwell time in the oral cavity can further be challenging as the drug can be rapidly eliminated due to the flushing action of saliva. As a result, repeated and frequent doses may be needed, unless the dosage form creates a strong bond with the absorbing mucosa. Research is needed to quantify how much salivary flushing affects the efficiency of oral transmucosal delivery from different drug delivery systems.

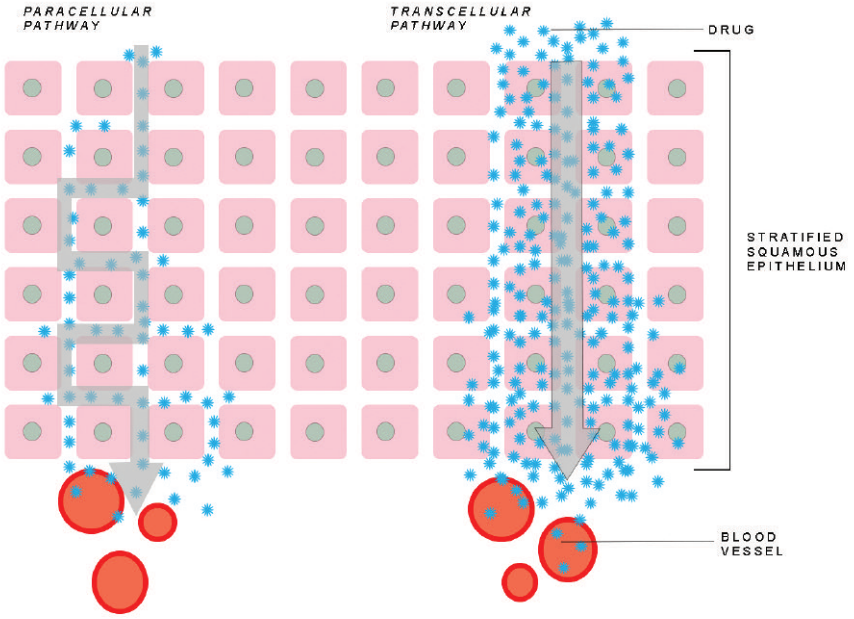
Human factors are important to take into account when developing a buccal product. Given that the buccal mucosa extends from the upper and lower spaces between the cheeks, lips, and gums, the precise location where the patient places the dosage form may affect the adherence and absorption of the drug, and these human factors implications can affect inter-patient variability. How the dosage form is placed can cause additional complications when the dosage form is designed for unidirectional release and has a specific adhesive side to be placed against the inner cheek. Lastly, when and what the patient eats, drinks, or smokes can further affect the absorption of the drug through the mucosa.

The risk of dislodgement and patient variability due to saliva stimulation can be minimized if the drug is administered over night for example, when the patient is not eating or speaking.

Buccal Dosage Forms

Although the buccal mucosa is only now being extensively studied as a novel drug delivery route, its potential for drug delivery has been known to mankind for centuries. Native Americans introduced chewing tobacco to European settlers in the 1500s, and coca leaves were chewed 8,000 years ago by Peruvian foragers. The buccal mucosa has been targeted using conventional dosage forms, such as tablets, troches and lozenges, and mouth washes and sprays, with several such

FIGURE 2



products currently on the market. The challenge is in holding these dosage forms at the site of absorption, dosing precision (liquids) and discomfort (tablets). Tablets have the potential to separate from the mucosa, be swallowed, and then adhere to the wall of the esophagus causing a choking hazard, especially for children and the elderly.

More advanced drug delivery systems include films, patches, bilayer tablets, hydrogels, and tapes along with the use of micro- and nano-particulates are being developed to overcome the limitations of conventional dosage forms.

FILMS FOR BUCCAL DELIVERY - CUREFILM

Mucoadhesive films are a preferred dosage form for buccal mucosa administration given their flexibility, comfort, palatability, and adjustable size. They have demonstrated improved patient compliance compared to adhesive tablets.[10,11] In contrast to liquid, gel, and ointment formulations, mucoadhesive films stay in contact with the mucosa longer, cover a larger surface area, and therefore provide more accurate drug dosing.[12] Indeed, mucoadhesive films can be designed through careful material selection to maintain extensive adhesive contact with the mucosal membrane, prolonging the retention time of the delivery system for increased total drug absorption. Furthermore, mucoadhesive films are well suited for local therapy, protecting oral wound surfaces from infection for example.[13]

Film compositions are designed to achieve the following physical properties: bioadhesive strength, tensile strength, pliability, flexibility, and extended disintegration. These properties are critical to achieve the target drug- release profile, patient acceptability, and compatibility with commercial manufacturing processes. Achieving the target specifications of buccal polymeric films is highly dependent on the type and concentration of the selected polymers and the dose of active ingredients being delivered.

As discussed here, even with a strongly adhesive film, the salivary flush will cause part of the film to dissolve in the oral cavity and be swallowed. Dual- layer films with an occlusive backing layer have been designed to drive unidirectional drug release and absorption into the buccal mucosa and can deliver high doses of active ingredient. While such designs can improve buccal absorption, they present several drawbacks. They can lead to user error in their application, the occlusive layer can dislodge and become a choking hazard, and lastly, the complexity of scaling up a dual-layer film drives up manufacturing costs.

Taking these constraints into consideration, CURE Pharmaceutical's approach to buccal film development with CUREfilm leverages the inevitable salivary flush of a single layer film to create better drug-release profiles. We design our products to combine the fast onset bolus effect of buccal delivery with the extended release of GI delivery to achieve an overall pulsatile- or sustained- release profile. Indeed, with buccal delivery, blood levels can peak quickly, and a shorter half-life can mean the effect wears off rapidly. Also, if delivering high doses of a drug solely buccally (eg, over 100 mg), the local tissue concentration could be too high and damage the tissue. A single layer approach is preferable as it minimizes costs and user error.

To create a buccal CUREfilm, a carefully selected blend of polymers, permeation enhancers, and lipids are combined to optimize adherence, drug diffusion, and permeation through the mucosa. Lipids play a crucial role in solubilization and stability of active ingredients. They help drive hydrophilic compounds through the mucosal epithelium and promote trans-cellular transport of lipophilic compounds through the epithelium to reach the blood vessels. Nano-particulation of the active ingredient

can provide an additional arrow in the formulator's quiver to increase the rate of absorption.

To achieve sufficient gastric protection and efficient intestinal release of the portion of drug that is swallowed, drug particles can be fully or partially encapsulated, enteric coated, or cross-linked to polymers, such as chitosan, prior to their incorporation into the film matrix. Other strategies include liposomal or micellar formation, co-crystallization, and the use of gelling or swellable polymers.

This dual strategy can be very useful for combination drugs with different metabolic profiles in which one drug is prepared for buccal absorption (ie, if it has a high first pass effect), and the other is prepared for release in the GI.

SUMMARY

The actual design and construction of an oral film capable of effective therapeutic delivery can be challenging and requires the creation of new technologies. As a result of these innovations, buccal films are now a commercially viable dosage form that can solve many problems faced by the pharmaceutical industry, patients, and their caregivers. They will be able to replace daily injections, such as apomorphine shots taken by patients suffering from Parkinson's disease. They can improve the bioavailability of drugs, such as cannabinoids, potentially lowering their dose and psychoactive side effects. When rapid symptom relief is needed, they can deliver a bolus effect. They are a convenient alternative to unpalatable liquids for children and hard-to-swallow pills for the elderly.

Given the important unmet market needs they address, the rate of adoption of oral films has been high. Indeed, the global market was valued at $2.1 billion in 2017 and is anticipated to expand at a CAGR of 13% during the forecast period from 2018 to 2026.[14] This commercial growth of oral films, including buccal films, reflects the pharmaceutical industry's increased focus on patient-centered innovation in the development of new medicines and the improvement of old medicines – where patient experience drives drug delivery design, which in turn improves patient outcomes. ◆

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BIOGRAPHIES

Robert Davidson is CURE's CEO and Chariman of the Board of Directors. Prior to his role at CURE Pharmaceutical, Robert Davidson served as President and Chief Executive Officer of InnoZen Inc., Chief Executive Officer of Gel Tech LLC, Chief Executive Officer of Bio Delivery Technologies Inc., and has served on multiple corporate boards. Mr. Davidson was responsible for the development of several drug delivery technologies and commercial brand extensions. He has a Masters Certificate in Applied Project Management from Villanova University, Masters of Public Health from American Military University, Virginia and a Masters in Health and Wellness from Liberty University, Virginia. Davidson also completed his Post Graduate Studies at the University of Cambridge with letter of commendation.

Jessica Rousset is CURE's Chief Operating Officer. Mrs. Rousset oversees operations and drives corporate strategy and growth. Mrs. Rousset previously served as Head of Innovation at Children's Hospital Los Angeles, where over a ten-year period, she helped launch both therapeutic and medical device companies and founded and operated a national pediatric technology accelerator. Prior to that, Mrs. Rousset held positions at The Scripps Research Institute and GlaxoSmithkline Biologicals in laboratory, clinical research and business development roles. She trained as a biochemical engineer at the Institut National des Sciences Appliquées in Lyon, France.

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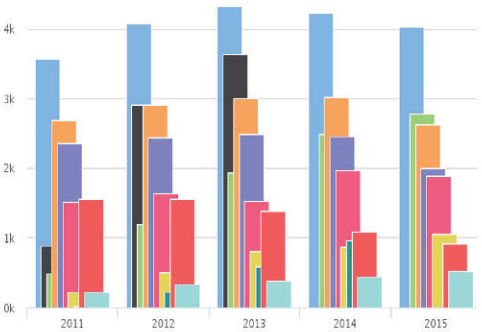

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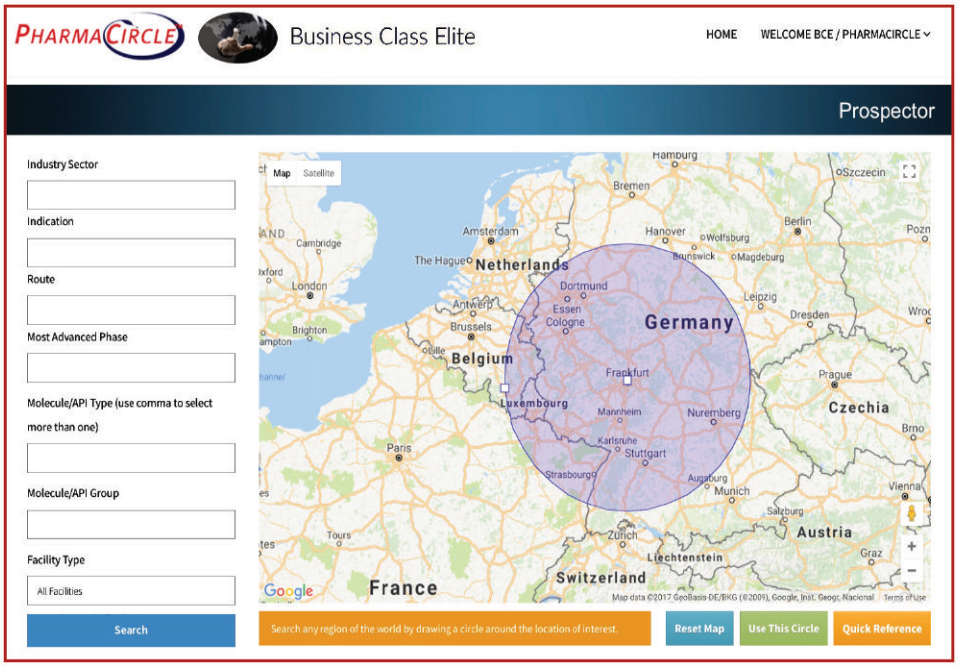

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Effect of Skin Model on In Vitro Performance of an Adhesive Dermally Applied Microarray (ADAM™) Coated With Zolmitriptan

By: Hayley Lewis and Mahmoud Ameri, PhD

INTRODUCTION

The in vitro human skin finite dose model, Franz, has demonstrated effectiveness in evaluating percutaneous absorption and assessing the pharmacokinetics of topically applied medicines. The model utilizes ex vivo human skin affixed to a bespoke diffusion cell that allows the skin to be kept at a temperature and humidity representative of in vivo conditions.[1] A finite dose (eg, 2 mg/cm^2-10 mg/cm^2 of a semisolid or a transdermal delivery system) of a formulation is placed onto the exterior surface of the skin and drug absorption is quantified by measuring the amount in the receptor solution. The total absorption, absorption rate, and skin content can be evaluated in this model. The method has precedent for accurately estimating in vivo percutaneous absorption kinetics.[2,3] The Franz cell has been utilized to evaluate microprojection facilitated drug delivery, employing ex vivo skin of varying thickness as the diffusional barrier.[4,6] Artificial membranes, eg, Silescol®, have also been proposed as a potential substitute to ex vivo skin.[7,8] The apparent benefits of employing artificial membranes are their availability, ease of use, and ease of storage. They may also lessen the variability concomitant with the use of ex vivo skin.[9] Although artificial membranes may have some benefits over human skin, definite correlation to human stratum corneum barrier function has not been completely explored, particularly for finite dose applications.[10]

In the present study, we assessed Strat-M (artificial membrane), full-thickness, and dermatomed ex vivo skin on percutaneous delivery of zolmitriptan from innovative drug-coated dermally applied microprojections that target the epidermal/dermal layer for fast and efficient delivery.[11] The Adhesive Dermally-Applied Microarray (ADAM™) system is composed of a titanium microprojection array adhered to an adhesive backing held in a retainer ring, and an applicator (Figure 1a). The adhesive backing in the retainer ring is docked to the applicator. The applicator (Figure 1b) is actuated through a spring force, which breaks the adhesive from the retainer ring and applies the patch onto the skin site. The drug-coated microprojections physically break through the stratum corneum and penetrate into the epidermis and dermis, where the dry drug coating is dissolved by the surrounding skin interstitial fluid. The ADAM system was recently evaluated in a Phase 2 clinical study with the delivery of zolmitriptan for the treatment of migraines.[12]

TABLE 1

Parameter	Mean Zolmitriptan (%) Dermatomed Skin	Mean Zolmitriptan (%) StratM®
Receptor	85.46 ± 1.36	10.55 ± 6.15
Dermis	0.50 ± 0.04	---
Epidermis	0.43 ± 0.16	---
Stratum Corneum	0.13 ± 0.04	---
Surface Wash	2.57 ± 1.09	---
StratM® Extraction	----	39.76 ± 19.75
Ti Array	3.27 ± 0.36	52.79 ± 29.28
Total Recovery	92.35 ± 2.48	103.1 ± 9.2

Mass Balance Results as percent of applied dose (%) of zolmitriptan into and through ex vivo human dermatomed skin and Strat-M® membrane over 5 hours from a single application. Mean ± SE for skin (n=3 Donors with 3 replicates/donor) and Mean ± SD (6 replicates) for the membrane. (Results adapted from Reference 11)

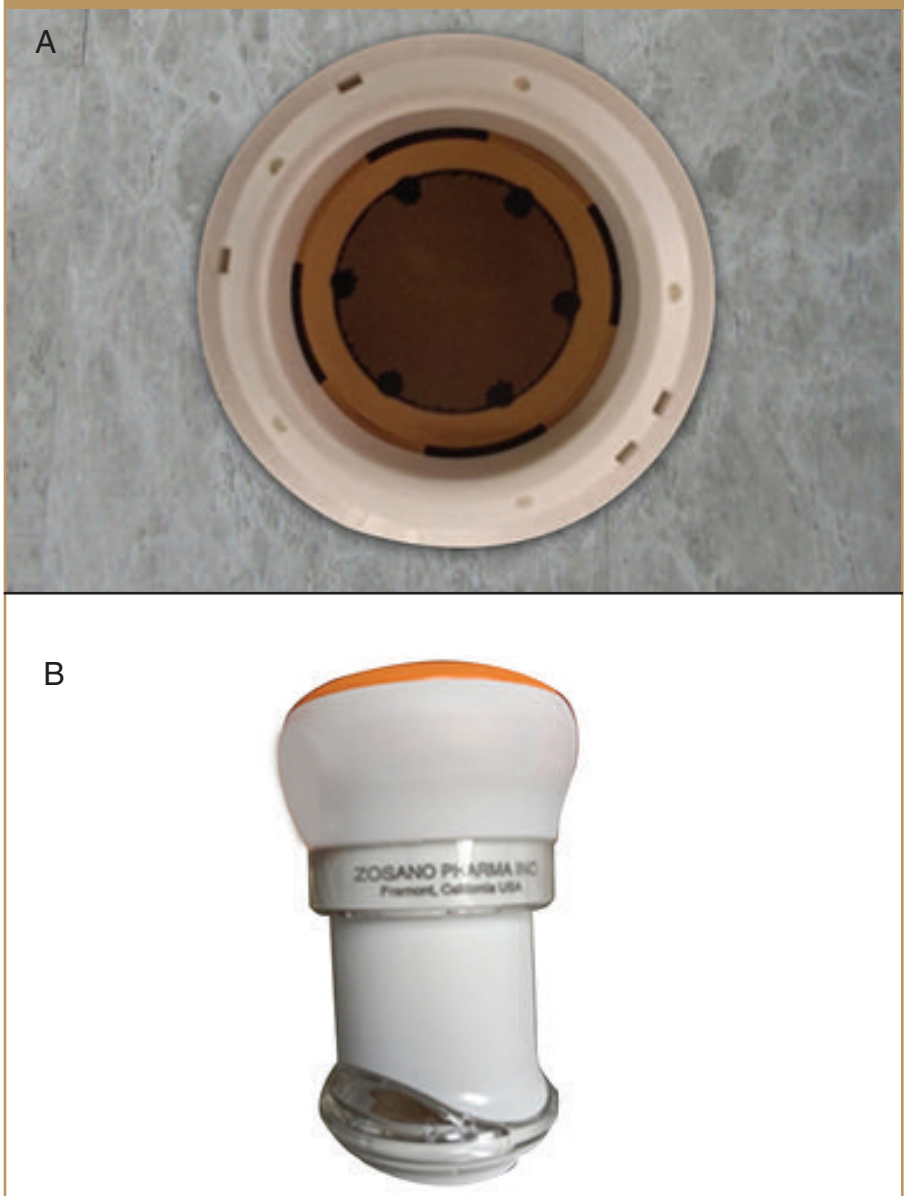
RESULTS

Franz cell experiments are typically employed to evaluate both in vitro bioavailability and bioequivalence of topical semisolid formulations and transdermal systems. One critical use of Franz cell experiments is to optimize formulations to improve percutaneous delivery.[14] Consequently, drug permeation through ex vivo skin should provide an estimate of in vivo percutaneous absorption. Nevertheless, the absence of a vascular system in an ex vivo environment signifies that the distance from the stratum corneum to its boundary with the receptor media may contain an additional unstirred barrier to drug permeation for some molecules. In an in vivo model, the distance is 200-400 µm from the stratum corneum to the dermis, where the greatest amount of drug is systemically absorbed via the capillaries.[15] Therefore, a crucial characteristic of an ex vivo percutaneous absorption experiment is a judicious consideration of the membrane utilized to model in vivo skin conditions.[14]

To assess the influence of the skin model on microprojection mediated delivery, full-thickness skin (0.70 ± 0.09 mm thickness), dermatomed skin (0.46 ± 0.09 mm) and Strat-M® (0.30 ± 0.01 mm thickness) were used. Figure 2 compares the percutaneous absorption of zolmitriptan through full-thickness and dermatomed ex vivo human skin over a period of 5 hours.

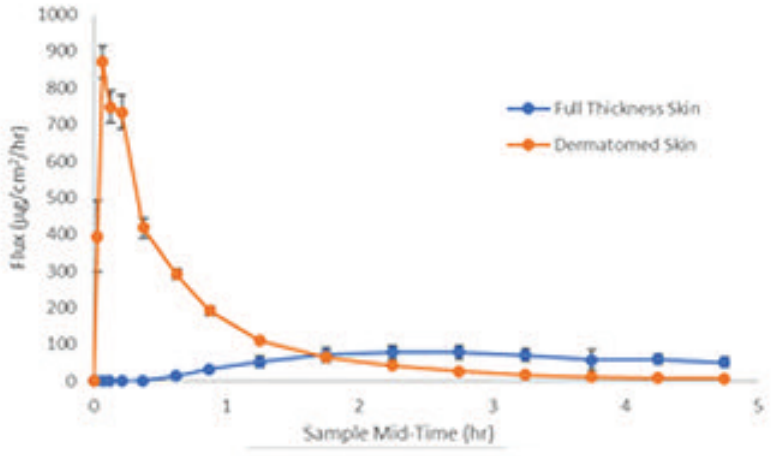
The absorption of zolmitriptan from the two skin sources are significantly different. The time to maximum flux was much slower with the full-thickness skin in contrast to the dermatomed skin. The time to maximum flux and the shape of the curve for the full-thickness skin substrate are in stark contrast to what has been conveyed by Kellerman, et al [16] in a Phase 1 clinical

FIGURES 1 A,B,C,D



Adhesive Dermally-Applied Microarray (ADAM) Zolmitriptan (a) 5 cm² adhesive backing with microprojection array (3 cm²) in applicator ring; (b) applicator ring press fit onto the bottom of the applicator; and applicator; (c) 60x magnification of zolmitriptan coated microprojections (725 microprojections/cm² and length 340 µm), Zolmitriptan coated at 1.9 mg/3cm² array; and (d) front view of an individual zolmitriptan coated microprojection (250x magnification). (Figure taken from Reference 11)

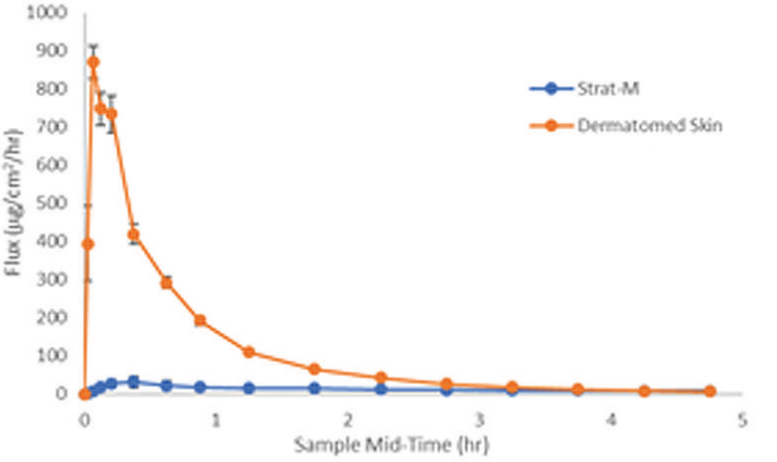
FIGURE 2



Comparison of mean flux (µg/cm²/hr) from full-thickness and dermatomed skin. (Results adapted from Reference 11)

study of ADAM Zolmitriptan, where the median Tmax was 20 minutes.[16] The distinction between the time to peak flux is that with in vivo skin, the apices of the microprojections are near to the capillary plexus of the dermis. This allows for fast release of drug into the blood stream compared to full-thickness in vitro skin that lacks the blood flow and results in the drug having to diffuse through the full dermis to the receptor solution. Utilization of dermatomed skin, where the lower region of the dermis at the capillary bed has been removed, is a better in vitro skin model because when the drug reaches that area, it finds the receptor solution rather than the capillary blood flow, which, in either case, provides sink conditions. The results show that the use of dermatomed skin resulted in the greatest extent of intracutaneous delivery in comparison to full-thickness skin. The data indicate that the diffusion of zolmitriptan across the full-thickness skin demonstrates how the dermis, without capillary flow, will result in a rate limiting step in absorption of microprojection facilitated drug delivery[17] attributable to the increased diffusional path length associated with the utilization of full-thickness skin.[17,18]

FIGURE 3



Comparison of mean flux (µg/cm²/hr) from Strat-M® synthetic membrane and dermatomed skin. (Results adapted from Reference 11)

Figure 3 compares the percutaneous absorption of zolmitriptan through Strat-M® synthetic membrane versus dermatomed ex vivo human skin over 5 hours.

The Strat-M membrane and the dermatomed skin permeation curve profile are analogous. However, the peak flux for the Strat-M is considerably lower than that of dermatomed skin. This singularity of low absorption across artificial membranes has been reported elsewhere and was associated with the high elasticity of the artificial membrane that causes the microprojections to retract, which means that the microprojections do not reside within the created conduits.[8] Similarly, adsorption of the zolmitriptan to components of the synthetic membrane, ca 40% of the applied dose recovered in the membrane versus <1% in the epidermal and dermal layers of the dermatomed skin, may also be a contributing factor. As a result, the use of Strat-M membrane inaccurately represents the absorption in vivo and can lead to a significant under estimation of the drug release profile.

Table 1 shows the mass balance of 1.9 mg ADAM Zolmitriptan that was applied to dermatomed skin and to Strat-M membrane. For dermatomed skin, the total recovery was 92% with total absorbed zolmitriptan of 85%. Negligible amount of drug was found on the stratum corneum and on the titanium array post administration. In contrast to the skin data presented in Table 1, the amount found in the receptor media for the Strat-M condition was ap-

proximately 11% of the nominal 1.9-mg zolmitriptan dose. Most of the dose resided on the titanium array (ca 53 %), and the remainder was on the surface or within the Strat-M membrane (ca 40%).

CONCLUSIONS

This study, the first to be conducted with microneedles coated with zolmitriptan, verified the effect of in vitro experimental conditions on the rate and magnitude of permeation of ADAM zolmitriptan. The outcome of the investigation indicates that artificial membranes such as Strat-M should be utilized with caution when assessing drug release from coated microprojections that are intended to deposit their drug locally via dissolution. Dermatomed skin may be a more representative measure of in vivo performance, not only for drug-coated metallic microprojections, but also a more representative approach for most in vitro absorption studies with this delivery system. The results of this study will further inform investigators with respect to modeling the in vitro performance of other formulations and their desired delivery profile, which can be used as a tool for screening prior to advancing to studies in humans. ◆

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BIOGRAPHIES

Hayley Lewis is the Senior Vice President of Operations at Zosano Pharma, where she oversees the functional areas of Nonclinical, R&D, Analytical Development and QC, Operations and Engineering, Manufacturing, and Regulatory Affairs, and continues to be responsible for overseeing all regulatory interactions with the FDA and other government agencies. She joined the company as the Vice President of Regulatory Affairs and Quality in October 2015. Prior to joining Zosano, she spent over 11 years in Regulatory Affairs at Depomed, Inc., a specialty pharmaceutical company, where she was involved in the approval of 3 commercial products. Over the course of her career, she has enabled 8 investigational products to be studied in humans, 5 of which have advanced to completion of Phase 3 trials. Her pharmaceutical development experience, spanning over 20 years, covers solid oral dosage forms, and combination products, such as systemic and local inhalation products, a single- entity combination injectable, and transdermal systems. Ms. Lewis earned her BS in Pharmaceutical Sciences from the University of Greenwich in England, and has attained several management diplomas from Kellogg School of Management, as well as Stanford's Graduate School of Business.

Dr. Mahmoud Ameri is the Vice President of Research & Development at Zosano Pharma. As one of the company's Co-founders, he brings 20 years of drug delivery, preclinical, and early ex US clinical development of combination products to the company. He is responsible for research and development. Prior to Zosano, he was at Alza/J&J where he co-invented and developed the Adhesive Dermally Applied Microarray system and holds over 20 patents and patent applications all relating to the Zosano drug delivery technology. Dr. Ameri earned his PhD from the School of Pharmacy at the University of Manchester in the United Kingdom.

ARTIFICIAL INTELLIGENCE

3Ds Powering AI in Drug Discovery – Domain Expertise, Deep Learning & Data

By: Liran Belenzon and Simon Smith

ABSTRACT

Artificial intelligence is attracting significant attention and investment for drug discovery. At least 97 relevant start-ups and 28 pharmaceutical companies use AI in some way. But not all applications are equal. Companies that combine domain expertise, deep learning, and proprietary data stand apart. In this article, we explore this combination in further detail. We counter skepticism about AI with concrete data on recent exponential progress. We provide examples of companies applying these advances to drug discovery. And we show how those combining domain expertise, deep learning, and proprietary data are excelling.

INTRODUCTION

In December 2017, a start-up of about 20 people did something unusual in drug discovery. After 15 months of starting a project, it was preparing a Phase 2a clinical trial.[1] This after identifying lead candidates, completing preclinical validation, and submitting a publication. Even more shocking: its budget was $100,000.[2]

The start-up, Healx (pronounced heal-ix), owes its efficiency to artificial intelligence (AI). It uses AI to repurpose and combine existing drugs to treat rare diseases. For this project, it focused on fragile X. It's the most common inherited cause of autism and learning disabilities. Affecting 1 in 4,000 males and 1 in 8,000 females, it's well-researched. But it still has no effective treatments. Thanks to Healx, it may soon. And more diseases could follow.

Healx demonstrates the power of combining domain expertise, deep learning, and proprietary data. The result is a scalable platform for drug discovery. But the model isn't confined to a single start-up, or start-ups in general. The "3D" approach is powering a new wave of AI-driven R&D. One that might (finally) achieve time- and cost-savings from the technology that the industry seeks.

HAVEN'T WE HEARD THIS ALL BEFORE?

To skeptics, this might sound like familiar AI hype. After all, the field has promised much since the 1950s. "We think that a significant advance can be made," wrote leading computer scientists in 1955 when proposing the first workshop on AI (a term they coined to describe the field), "if a carefully selected group of scientists work on it together for a summer."[3] A summer!

The exuberance earned the field funding in the 1960s. But disillusionment set in when the hype went unfulfilled. In the 1970s, funding dried up, beginning a so-called "AI winter." A shift to work on narrow, brittle rules-based expert systems dominated the 1980s. A few pioneers of today's neural networks persisted in more ambitious work, but at the margins.

In 1997, IBM rekindled public interest in AI with Deep Blue's victory over Garry Kasparov.[4] The media amplified the excitement, with headlines such as "The Brain's Last Stand."[5] But critics labeled it a victory of brute force computation, not intelligence.[6] The hype again deflated.

Beginning in the mid-2000s, public excitement swelled again. And this time, with more unequivocal success. In 2005, five robot cars completed DARPA's Grand Challenge after none did the year before (setting the stage for the coming self-driving

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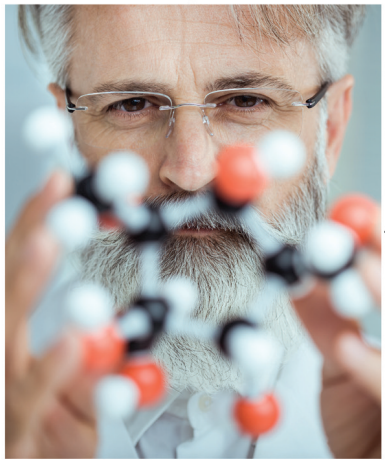

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car revolution).[7] The success came in part from advances in machine learning.

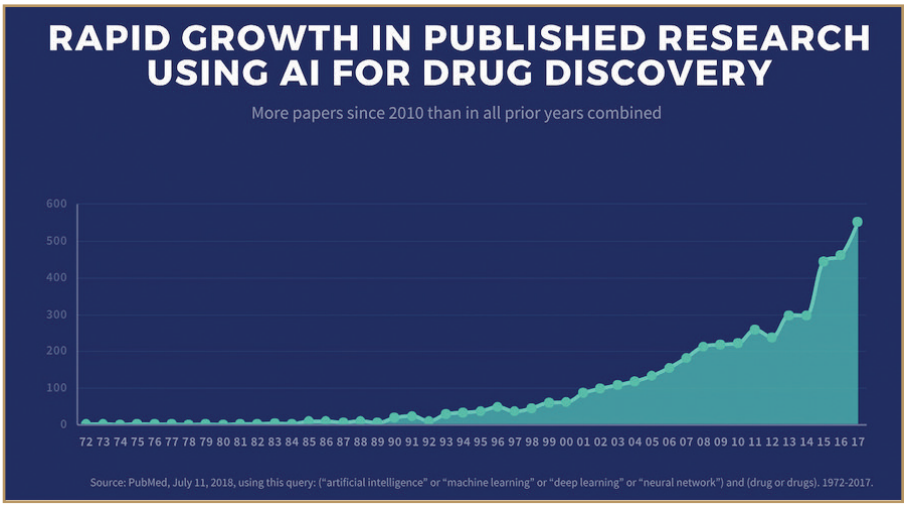
In 2011, IBM once again stoked people's hopes (and fears) about the potential of AI.[8] Its Watson system combined natural language processing algorithms to answer questions on Jeopardy! and beat the world's top players. Watson needed 90 servers to do it.[9] But unlike with Deep Blue, fewer critics denied it some claim on some form of intelligence.

But IBM's dominance of AI news was short-lived. In 2012, University of Toronto researchers changed the conversation — and the dominant algorithms.[10] Competing on a benchmark image classification task, their "AlexNet" system achieved unprecedented improvement. It did so using layers of connected artificial neurons running on graphics processing units (GPUs). Once confined to the margins, this approach, called deep learning, took center stage.

EXPONENTIAL GROWTH IN PERFORMANCE & PAPERS

Since then, progress has been exponential. In 2016, Google's DeepMind used deep learning in AlphaGo to beat top player Lee Sedol at Go.[11] A year later, it unveiled AlphaGo Zero, which taught itself to play Go, and beat AlphaGo.[12] Another variant, AlphaZero, beat a top-ranked chess program.[13] Processing power used in AlphaGo Zero was 300,000 times greater than in AlexNet.[14] It doubles every 3.5 months for the largest neural networks.[15] Performance on tough tasks such as image classification is keeping pace. Machines went from subhuman to superhuman in 5 years.[16]

This time, the hype seems justified. And drug discovery isn't immune. In fact,



there have been more papers on AI in drug discovery this decade than all prior years combined.[17] As recently as 1997, there were 36. Last year, there were 552, a greater than 15x annual increase in a decade.

And the advances aren't only in research. Start-ups and established companies are commercializing them. By our count, there are now at least 97 start-ups using AI for drug discovery.[18] We have also identified 28 pharmaceutical companies that have disclosed using the technology.[19]

Nor is this all vaporware. In addition to Healx, other companies have now progressed treatments discovered in silico. Companies with AI-driven therapies in trial include BenevolentAI, Berg, BioXcel, Lantern, and Recursion.[20-24] Many others have licensed promising compounds to pharma partners for development.

COMPLEMENTING ALGORITHMS WITH SPECIALIZED DATA & KNOWLEDGE

Deep learning is driving this process, but not alone. For one thing, deep learning benefits from lots of data. The benchmark database for image classification, for example, contains more than 14 million images.[25] Whereas a human child can point to a cat after seeing one example, today's machines cannot. They need thousands. For specialized applications, this data often doesn't exist. And if it does, often not in a format that's good for machine learning. Today's AI-driven drug discovery start-ups wouldn't be possible without specialized data. So they've invested in amassing it.

Along with deep learning and data, domain expertise has been essential. Technology start-ups whose leaders lack healthcare experience tend to underestimate their challenges.[26] These include not only technical hurdles, but also regulatory and cultural hurdles. As start-ups get more specialized, their need for specialized domain expertise does too. "Healthcare" is too general a domain if your focus is oncology. Oncology is too general a domain if your focus is immuno-oncology. And on it goes.

Healx is a great example. Its domain is repurposing and combining drugs for rare diseases. Expertise in this domain comes from leadership including drug discovery veteran Dr. David Brown, who is the co-inventor of Viagra, one of the most successful repurposed drugs of all time.[27] Deep learning powers Healx's platform,

HealNet, which predicts novel disease-drug relationships.[28] Data comes from public sources, such as research papers and clinical trials. But also proprietary sources, such as rare disease advocacy groups.[29] Combined, Healx's domain expertise, deep learning technology, and data assets have proven potent. In July 2018, investors recognized its potential with a $10-million investment.[30]

But Healx is far from alone. The trend amongst start-ups using AI for drug discovery is to increase specialization. In April, for example, MIT spin-out ReviveMed received $1.5 million in seed funding.[31] Its focus is metabolomics. Its founder is a domain expert, computational biologist Leila Pirhaji. Its competitive advantage is a proprietary metabolomics database and partnerships to grow it. Another example is CytoReason, whose founder is Shai Shen-Orr, a leader in the field.[32] Its focus is systems immunology, and its competitive advantage is a proprietary dataset including experimental data. The list goes on. Envisagenics for RNA.[33] BioAge for aging.[34] The future isn't IBM Watson designing everyone's drugs. It's the combination of specific expertise, technology, and data to solve specific problems.

A MANDATE FOR SUCCESS IN HEALTHCARE

Of course, if you're familiar with the concept of the "long tail," none of this should be surprising.[35] Low-cost digital technology is famous for allowing niche businesses to thrive. But there's more to this story.

Combining domain expertise, deep learning, and data isn't only trendy. It's a mandate. Without domain expertise, companies suffer. They don't understand the problem space or the drug discovery process. And they can be overconfident in technology's power to overcome non-technical challenges. This includes regulatory hurdles, privacy constraints, and the often slow pace of healthcare.

Without deep learning, it's too hard to extract value from large biological datasets. The larger and more feature-rich they are, the harder it gets.

And without such data, you can't maximize deep learning's potential. It's like filling a swimming pool with a few inches of water. Proprietary data is particularly important. Processing power and data storage are commodities. Software libraries for deep learning are free and open source. Large, free biology datasets are downloadable for all. Proprietary data is key to building and sustaining a competitive advantage. We learned all of this first-hand early in 2018.

OUR JOURNEY FROM THE LAB TO A GOOGLE INVESTMENT

At BenchSci, we decode the world's biological data to reduce the time, uncertainty, and cost of biomedical research. We use machine learning to read scientific papers and extract data on reagent use. Researchers can search BenchSci instead of PubMed when selecting reagents. Rather than using keywords, due to machine learning, they can search by protein or gene. And then they can filter by technique, organism, tissue, and 13 other options. Using BenchSci, researchers can select antibodies up to 24x faster. And they can shave months off an R&D project's timeline.

But as we learned, such product-market fit is only the starting point for investors. In early 2018, we met with 30 venture capital firms to raise a series A investment. These days, they see a lot of AI companies. And their feedback was unanimous. If an AI start-up has technical expertise but no domain expertise, they should get it. If they use machine learning but not advances in deep learning, they should apply them. And if they use only public data, they should develop proprietary sources. And, for good measure, a data feedback loop: using data to build a product that gathers data. Only then do they have a shot at big success.

We were lucky to pass these tests. Our CSO, Tom Leung, felt the pain of selecting reagents doing cancer research. He and our science team bring domain expertise. Our CTO, David Chen, applies his neuroscience background to develop machine learning advances. He and his team provide the deep learning. And our data comes from public sources, vendors, closed-access publications, and platform use. There's the proprietary data, and a data feedback loop for good measure. Only by clearing the hurdles could we earn investment. This included investment from leaders in AI, such as Google's AI-focused venture fund.[36]

PHARMA COMPANIES ARE CATCHING ON

But start-ups and investors aren't the only ones to have noted the importance of these factors. So have the world's largest pharmaceutical companies. Now they're reorganizing their business around domain expertise, data, and deep learning too.

Novartis CEO Vas Narasimhan, for example, is remaking the company around

"medicines and data science."[37] Novartis restructured its Global Drug Development (GDD) IT infrastructure, connecting disparate datasets. This includes 20 years worth of data from clinical trials. With the first phase of its project complete, it's now looking to apply machine learning. "What if we were to combine all our data sets together, access the data, and make it specific to disease areas so that scientists can ask the questions they weren't able to ask before?" said Achim Plueckebaum, Global Head of Drug Development IT, in a recent interview.[38] Jay Bradner, Head of the Novartis Institutes for BioMedical Research (NIBR), leads a similar charge.[39] He reports that 4% of NIBR's 6,000 scientists are now data scientists.[40]

GSK is undertaking a similar revamp.[41] John Baldoni, SVP, Head of In-Silico Drug Discovery Unit, has a rallying cry. He wants to go from target to treatment in 12 months (versus 6 years). Once again, domain expertise, data, and deep learning play a central role. GSK hired Chief Data Officer Mark Ramsey from Samsung. He led the consolidation of 2,500 distinct structured data sources. And GSK established partnerships with start-ups that leverage deep learning in different domains. Several intend to find new uses for GSK's now-consolidated proprietary data.

SUMMARY

So, whether you work in a start-up or a large pharmaceutical company, the trend seems clear. This time, the hype over AI seems justified. But not everyone will reap equal benefits. Emerging winners have a few things in common. They focus on specific applications and are experts in their domain. They apply deep learning advances to extract value from large, feature rich datasets. And they develop proprietary, domain-relevant datasets, often with feedback loops.

If this sounds like your company, you have a good shot at success. If not, get inspired! Researchers are already using AI to develop drugs in months, not decades. For hundreds of thousands of dollars, not billions. And with AI, progress is exponential. Processing power for the largest neural networks will double in 3.5 months. So what are you waiting for? ◆

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BIOGRAPHIES

Liran Belenzon is Chief Executive Officer of BenchSci, which is decoding the world's biological data to reduce the cost, time, trial and error, and redundancy of biomedical research. Prior to BenchSci, he co-founded Israel's first B2B e-commerce marketplace. He also served as a commander in the Israeli Defence Forces. He is passionate about using data and algorithms to improve reproducibility, efficiency, and cost-effectiveness in drug discovery. Mr. Belenzon earned his MBA from the University of Toronto's Rotman School of Management.

Simon Smith is Chief Growth Officer at BenchSci. Prior to BenchSci, he was SVP, Strategy at Klick Health, where he consulted on digital strategy for the commercialization of drugs in neurology, gastroenterology, endocrinology, and oncology. During this time, he led digital strategy for two US drug launches: a novel antidepressant, and a novel biologic for inflammatory bowel disease. Mr. Smith earned his undergraduate degree in Journalism from Ryerson University, and his Master of Arts in the History and Philosophy of Science and Technology from the University of Toronto.

Drug Development
EXECUTIVE

Sameer Navalgund
Global Director
JRF Global

JRF GLOBAL

JRF Global: Innovating Drug Discovery & Development Solutions for Your Leads

Typically, drug discovery is a large segment for the CRO industry. If the CRO industry is categorized by the therapeutic area, then oncology, diabetes, tuberculosis, cardiovascular diseases, infectious diseases, central nervous system-related disorders, and respiratory diseases take up a larger pie of the industry services. However, innovative technologies, including the organ-on-chip, are increasingly attracting a lot of attention and efforts, and the CRO industry can contribute significantly to these newer trends. Sameer Navalgund, Global Director at JRF Global, shares his perspective with Drug Development & Delivery about the on-going trends, current status, and some of the upcoming biggest challenges in the contract services industry.

"JRF Global operates in multiple geographies with a diverse customer base. Therefore, there is no single strategy; it depends on the geography and customer we service. However, to answer the question in a comprehensive manner, I would say the key areas of strategy are innovation, growth, and sustenance."

Q: Can you describe the current status of the contract services industry? What trends are you seeing?

A: For the past few years, the CRO Industry has undergone a lot of activity related to mergers and acquisitions. Historically, the CRO market was fragmented, but these increased merger and acquisition activities have led to some consolidation. I expect to see similar trends for some time. Earlier, some of the declining growth in the pharma/biopharma industry market had affected the CRO industry. Due to shrinking growth rates, some pharma/biopharma companies needed to lower their drug development costs. Therefore, many of them looked at various cost-saving options, including out-sourcing. This trend is expected to increase in the near-term. Typically, drug discovery is a large segment for the CRO industry. If we categorize the CRO industry by the therapeutic area, then oncology, diabetes, tuberculosis, cardiovascular diseases, infectious diseases, central nervous system-related disorders, and respiratory diseases take up a larger pie of the industry services. In my opinion, these trends will continue in this direction for some time to come. Newer technologies, including the organ-on-chip, will also continue to attract a lot of attention and efforts, and the CRO industry can contribute significantly here as well.

Q: What do you believe are some of the biggest challenges in the contract services industry?

A: For some time now, the HR departments in the majority of industries have to operate in a VUCA world, where VUCA stands for Volatility, Uncertainty, Complexity, and Ambiguity. In my opinion, the science equivalent of it is UVCB (Unknown or Variable composition, Complex reaction products, and Biological materials). Understanding the nature and properties of such compounds that are presented by the customers to the CROs is one of the biggest challenges. In some cases, "it feels like they expect a lab to help them resolve the issue while they don't know the problem," as a CRO colleague would put it mildly. I believe this will continue to be a challenge, and a deeper understanding between the customer and the CRO would help resolve this to a larger extent. Rather than working as a customer and vendor, we will have to work as partners. In terms of the business challenge, to keep the staff motivated with challenging work, we believe using a grow-sustain model at the appropriate time, continuing innovating, and ensuring timelines are met with quality will be the biggest challenges facing the contract services industry.

Q: Can you provide our readers some history of the company and an overview of your business today?

A: JRF metamorphosed in the 1980s from erstwhile Phospho laboratory with the vision to serve the nation by providing quality services in the field of Research & Development. It received its very first accreditation in 1987 from the then NCTCF (today's DST – Department of Science and Technology, Government of India). Initially, the focus areas were toxicology and agrochemicals. Over a period of 4 decades, it has evolved in a global organization with operations on four continents and customer-focused business interests throughout the world. Today, JRF Global serves a diverse spectrum of customers from pharma/biopharma to specialty chemicals and agrochemicals with expertise in toxicology, chemistry, and biology-based services.

Q: What does JRF Global offer when it comes to contract research services, especially in Drug Discovery and Development ?

A: JRF, as a leading CRO, offers a variety of services to the pharma/biopharma industry. As a part of our Drug Discovery and Development Services programs at JRF Global, we offer early ADME, efficacy models, impurity profiling, exploratory toxicology, PK/TK, and metabolism and metabolite characterization. JRF Global's IND-enabling safety evaluation expertise also encompasses a wide range of services starting from impurity profiling; genotoxicity; safety pharmacology (for *in*

vivo CNS, CVS, & respiratory and for *in vitro* hERG assay); a special mention is for the dog telemetry and whole body plethysmography and modified Irwin test for rodents and non-rodent repeat dose toxicology by multiple administration routes like oral, dermal, parenteral, ocular, and inhalation; reproduction toxicology; and carcinogenicity during the preclinical stage of drug development.

Q: Are there particular services that distinguish JRF Global? Why do pharma/biopharma companies choose to work with JRF Global?

A: In my opinion, all the services at JRF Global are distinguishing factors for all of our customers. When it comes to pharma/biopharma companies, I can broadly classify JRF Global's distinguishing factors in the following areas:

Scientific human resource, know-how, experience, and training: Our teams, led by PhD scientists provide guidance to support pharma companies' submissions. JRF Global's scientific teams have hundreds of "man" years of experience in conducting chemical characterization as well as preclinical studies, specifically focused on proving data for the safety and efficacy of the compounds to assure the regulatory bodies, to receive the permissions for first-in-man trials. We strive to ensure these teams remain updated about the recent developments by actively participating in various conferences, seminars, and training programs. Many of our valuable customers have successfully submitted their INDs to the FDA, EMA, and other regulatory bodies throughout the world.

Laboratory infrastructure: We believe in having updated and state-of-the- industry laboratory infrastructure. Technology and automation are the keys to work for the future. This keeps us ahead in terms of various developments in the scientific fields. We strive and keep ourselves abreast with modern technology, equipment, and their use. We are proud to have one of the best animal houses as well as excellent breeding facility for select species. We are also working very rapidly for SEND compliance.

Quality: JRF Global's Quality Assurance Unit ensures that all the efforts of the organization are in compliance with the required regulations. This team actively follows any change in the guidelines and standards, and then makes the required change at JRF Global using our change control and management processes to implement them. However, this does not mean that it's the QAU that is responsible for the quality, it is the responsibility of all "JRFians" collectively, and we work hard to make it a part of our "muscle memory', if I may say so.

Timelines: These are the most critical for IND submissions and hence, JRF Global has adopted innovative system for accelerated IND evaluation and submission summary reports, as well as audited draft reports in order to enable customers to plan their submissions in advance. JRF Global's custom-built software and data-bases help in tracking and ensuring that customers receive all inputs in-time. The project management and business development teams are the Customers' Ambassadors at JRF Global, and they ensure these customers' needs are met and addressed.

Innovation: At JRF Global, we have dedicated teams to research and develop new assays, tests, methods of analysis, and molecule synthesis, and continually review new scientific developments in the pharma/biopharma space. Upon successful completion, these teams implement and teach other colleagues these newer and modern services that help our pharma/biopharma customers. I call this JRF Global's Innovation center. These teams are the (new) pathfinder for us.

I can add an example here. With an increasing demand for respiratory therapeutics, it has become an imperative subject to assess the safety of the test item or device before they are used for therapeutic indications. JRF Global's Inhalation Toxicology Facility is designed to provide contemporary capabilities for conducting exposure of experimental animals under the Good Laboratory Practices (GLPs), providing contemporary capabilities for conducting exposure of experimental rodents under GLP. Each protocol for such studies is approved by the Institutional Animal Ethics Committee (IAEC). The nose-only equipment allows for higher density of rodents exposed in parallel. Over the years, JRF Global has acquired enormous experience of handling different types of chemicals. More than a thousand inhalation exposure studies have been completed in compliance with GLP and submitted to several regulators throughout the world, and our studies are well-received by global regulators.

Q: What is JRF Global's business strategy?

A: JRF Global operates in multiple geographies with a diverse customer base. Therefore, there is no single strategy; it depends on the geography and customer we service. However, to answer the question in a comprehensive manner, I would say the key areas of strategy are innovation, growth, and sustenance.

I strongly believe in innovation to maintain JRF Global's competitive advantage. Our research and development teams strive to innovate new methods, ways, and tests for a variety of matrices and active ingredients by multiple chemical and in-vitro biological experimentation. This helps JRF Global create new services to cater to diverse customer needs. These additional services bring in growth in terms of services offered, sectors of industry served, and newer technology investments. The last bit is the growth path we take by driving various strategic initiatives to their logical conclusions. As an organization, I also look at strategic acquisitions that will augment the capacities and capabilities of JRF Global. JRF Global strives to serve with timeliness and quality that gains us the confidence of our customers, and they work with us for longer term duration. Sustenance of the organization for serving our customers over a period of time is essential as they may get regulatory or other queries, and JRF Global would be supporting them to answer those queries. Therefore, sustenance is an important piece of the strategy for us.

Q: What is the typical JRF Global customer?

A: Our customers come from varied backgrounds and businesses. Some of them are brilliant studio companies with lots of ideas, innovators, generic companies, domestic, and large multi-national conglomerates. So the range is very wide and so are the associated challenges with respect to their expectations. We treat each and every customer for their individuality and uniqueness. We work with them and provide tailor-made solutions. One common aspect in this diversity is their expectations for their studies to be done on time and with higher quality. This keeps us on our toes in terms of project deliveries and quality of output. We do justice to meet their needs. ◆

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MARKET BRIEF

Alzheimer's Disease Market Report (2016-2026)

By: Akiko Fukui, MSc

INTRODUCTION

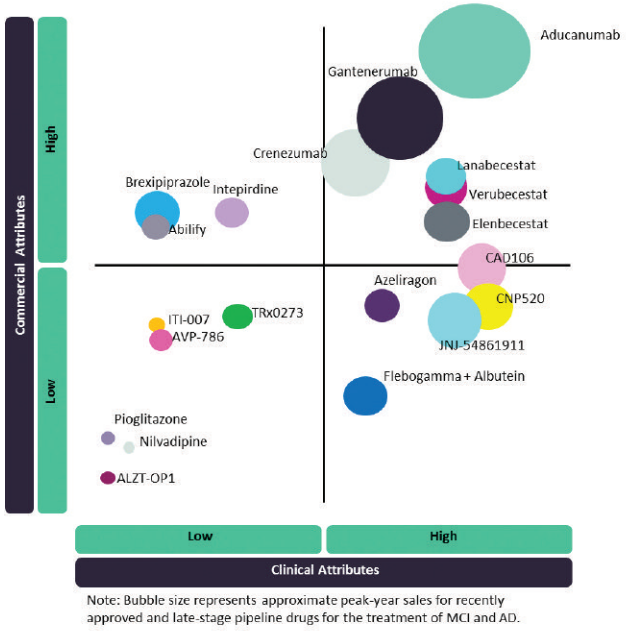
The race to develop the first disease-modifying drug for Alzheimer's disease (AD) is fierce. Despite the fact the number of people with AD is projected to rise sharply in the coming years, no new drug has been approved in more than a decade. Even the most recently FDA-approved AD product, Namzaric, is a combination of the two commonly prescribed AD drugs donepezil and memantine, and the added value of the product in the clinical setting is questionable as many physicians prescribe the cheap generic versions of the two drugs in combination already. With a failure rate of 99%, the AD market has been described as a graveyard for drugs. However, amid several failures, the AD pipeline is large and consists of many novel mechanisms, which makes it an exciting market undergoing rapid changes despite its high risk. There is strong sales potential in the market given the global aging population, growing public awareness, and advancing diagnostic capabilities, which drive pharmaceutical manufacturers to take the risk to pursue their quest to find new drugs for AD.

ALZHEIMER'S DISEASE MARKET FORECAST

GlobalData estimates sales of AD therapeutics in 2016 to have been approximately $3 billion across the seven major markets (7MM), which are the US, the five major European markets (5EU: France, Germany, Italy, Spain, and UK), and Japan. By 2026, GlobalData anticipates the AD market will have grown at a strong Compound Annual Growth Rate (CAGR) of 17.5%, reaching sales of $14.8 billion across the 7MM. This is mainly attributed to the growing prevalence of both AD and mild cognitive impairment (MCI) and the rapid uptake of biologics and other novel disease-modifying therapies (DMTs).

Throughout this forecast period, the most prominent contributor to sales will be the monoclonal antibody-based immunotherapies and the BACE inhibitor class, which are expected to reach $7 billion and $1.9 billion, respectively, in global AD sales by 2026. These drug classes are designed to target the disease at very early stages of development and are thereby expected have therapeutic as well as preventative benefits in patients with MCI or AD, as well as in healthy individuals at increased risk of de-

FIGURE 1



Competitive Assessment of Late-Stage Pipeline Agents in AD, 2016-2026

FROST & SULLIVAN

What do you *really* know about end users of drug delivery technologies?

Drug delivery technologies are a vital component of the dynamic Life Sciences industries, but how well does your company understand the end-user's perspective on desired attributes, compliance issues and drivers of adoption/non-adoption for different drug delivery types?

Frost & Sullivan's Life Sciences experts can provide your organization with the research and tools necessary to fully understand your customers as well as identify and take advantage of the best opportunities for growth in the drug delivery technologies market.

Our expert healthcare analysts:

- Identify growth challenges and optimal growth strategies
- Evaluate each strategy to identify those producing the best ROI
- Develop client-tailored, effective implementation strategies

For more information on how to find growth opportunities in the drug delivery market, please contact Mireya Espinoza at mireya.espinoza@frost.com or **210-247-3870**.

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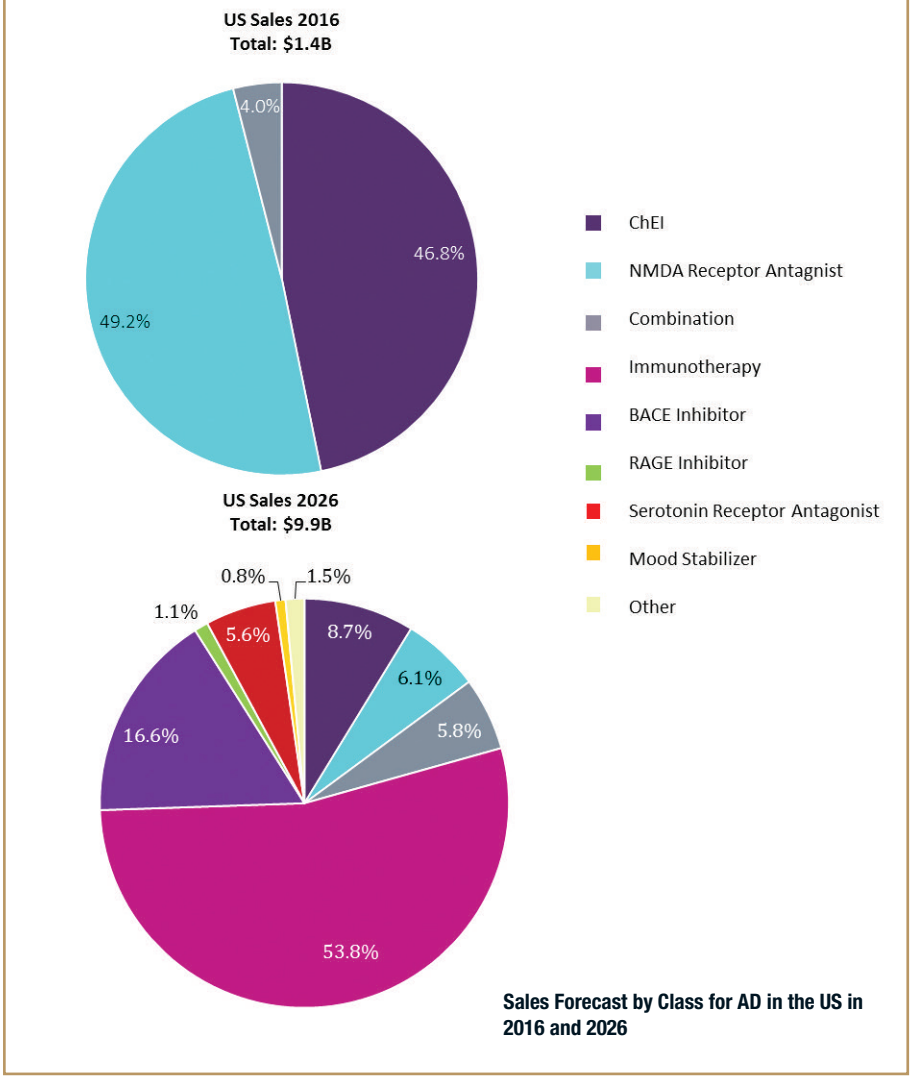
FIGURE 2



Sales Forecast by Class for AD in the US in 2016 and 2026

veloping AD. The launch of aducanumab, the first-in-class amyloid-beta (Aβ)-targeting immunotherapy, will be a key driver of AD market growth, as its sales are projected to peak at $3 billion by 2026. Moreover, subsequent immunotherapy and BACE inhibitor launches, as well as an increase in the global prevalence of AD, will continue to strengthen the sales growth.

The combined AD and MCI populations in the 7MM are expected to reach approximately 48 million people by 2026, which represents an annual growth rate of 2.3% from 2016. In the 2016 base year, 34.5% of market share ($1.1 billion) was attributed to mild AD, which generated the highest sales out of all AD severity groups. By the end of the forecast period, GlobalData anticipates MCI will contribute the largest share, with sales attributed to this group reaching almost $6.8 billion (46%) by 2026 due to the introduction of DMTs.

HOW WILL THE AD TREATMENT LANDSCAPE CHANGE?

The treatment of dementia and symptoms associated with AD has stayed relatively stagnant for some time. The treatment of AD is only offered through the management of symptoms, and no drug is available to slow down, halt, or reverse the process of neurodegeneration, which causes the symptoms associated with AD. The most commonly prescribed treatment across all severity groups is Aricept (donepezil), while for severe AD alone, Namenda (memantine) is the treatment of choice. Although these two drugs are the standard of care across the 7MM, sales for these products are slowly declining, with their patents expired in most of the 7MM and physicians and patients observing little symptomatic benefit.

Since the launch of Namzaric (donepezil + memantine) in the US in 2016, its sales have steadily increased and are expected to continue growing, with peak sales forecast to be $574.1 million in 2025, when its patent is expected to expire. Although Namzaric's sales are expected to drop from that point, with generic versions rapidly becoming available, overall sales during the forecast period are expected to grow at a CAGR of 26.3%, the highest growth rate of all the branded AD drugs. It is currently unclear whether Namzaric is going to be launched outside of the US.

Throughout the 2016-2026 forecast period, a number of pipeline products are expected to enter the market. The most promising of these is aducanumab, an Aβ-targeting immunotherapy being developed by Biogen. It is expected to reach the market by 2020, after which it is forecast to reach global sales of $3 billion, becoming the highest-selling drug for AD. Verubecestat and lanabecestat are BACE inhibitors, a novel drug class that has been shown to interrupt the Aβ production pathway, and are predicted to launch at similar times in 2020. Verubecestat and lanabecestat are forecast to yield $492.1 million and $552.9 million in global sales by 2026, respectively. Although sales of BACE inhibitors are forecast to be significantly

lower than those of immunotherapies due to the large expected price difference, BACE inhibitors are expected to be prescribed widely due to their simple oral administration and more affordable cost.

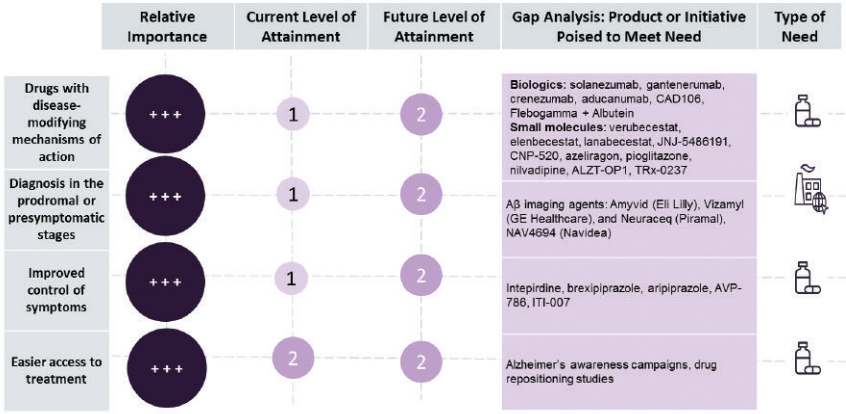
In addition to immunotherapies and BACE inhibitors, a range of drug classes are also aimed at modifying the disease; these include PPAR-gamma agonists, RAGE inhibitors, calcium channel blockers, and tau aggregation inhibitors. With rapidly improving AD clinical trial designs and biomarkers incorporated into the trials, drugs targeting additional novel targets are likely to emerge.

WHAT OPPORTUNITIES REMAIN?

Despite significant advancement in AD research, physicians interviewed by GlobalData identified a number of key clinical and environmental unmet needs in the field. They include drugs with disease-modifying mechanisms of action, improved control of symptoms, and lack of biomarkers for early diagnosis.

The lack of DMTs remains a significant unmet need. The current competitive landscape in AD offers medications that are aimed at treating the symptoms of the disease, which are modestly effective and primarily off patent, leaving ample room for new entrants into the AD market. Despite the past failures, knowledge in the field has rapidly improved, and many of the physicians interviewed agreed that the first DMT for AD will most likely be approved within the next 5 to 10 years. The need to prevent the onset of AD has prompted several different research collaborations, such as the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU). Significant

FIGURE 3



Unmet Need & Opportunity in AD, 2017

opportunities remain for small- and medium-size companies as well as institutional research teams to collaborate to gain insights for their drug development. Moreover, there are opportunities for companies to enter licensing deals, as many are looking to expand their product portfolios while smaller companies look to gain access to the facilities and resources that larger manufacturers offer.

The symptomatic relief offered by the current treatment options is limited, and off-label products, such as sedatives and antipsychotic medications, can be dangerous in elderly patients. Given the multitude of symptoms associated with AD, and because caregivers often experience great difficulties caring for patients when they are agitated or demonstrating behavioral issues, symptomatic treatments are a vital part of AD treatment regimens. Because symptoms such as agitation are still poorly treated, opportunities remain for drugs that can target these poorly targeted symptoms. Opportunities for symptomatic drugs are likely to remain because there are many FDA-approved drugs that can potentially be repurposed for AD, and symptomatic drugs will continue to be prescribed as additional treatments even when DMTs become available.

As the focus of AD pharmacotherapy shifts to the early stages of the disease, biomarker development has become an increasingly important area of unmet need, both environmentally and clinically. AD presents a diagnostic challenge in that patients remain asymptomatic while the underlying pathologic changes begin to take place. Amyloid positron emission tomography (PET) imaging is, at present, the furthest developed biomarker for AD, and this satisfies the unmet need to some extent. However, the need for simple, inexpensive, and non-invasive tests remains, and current imaging tools need to be refined so that their sensitivity and specificity can be improved. Great opportunities remain for the development of diagnostic methods through cerebrospinal fluid (CSF) analysis, blood-based tests, and medical devices, which will make early diagnosis accessible both for patient enrollment in trials and for clinical treatment.

WHAT DO PHYSICIANS THINK?

Physicians interviewed by GlobalData were cautiously optimistic about future drug development in the AD therapy area. There was a common optimism toward the main mechanisms of action currently being explored, namely Aβ-targeting therapies, including immunotherapies and BACE inhibitors. However, most KOLs also showed concerns due to the current lack of evidence:

"I still think this story holds a lot of promise. I wouldn't want to say I'm optimistic, that would be crazy given the field has seen so many setbacks. However, amyloid-targeting therapies are still showing encouraging results." - OUS Key Opinion Leader

"In my opinion, aducanumab is the most promising in development. I've seen very encouraging early phase data to support the view that aducanumab is highly effective at clearing fibrillar A in the brain and maybe that in doing so, has some cognitive benefits." - OUS Key Opinion Leader

"I think it's a good chance to try some preventative treatment with asymptomatic people, but I think that the design of the trial will be very difficult because we don't know if asymptomatic treatment will develop Alzheimer's disease and for how many years do we have to do this kind of treatment?" - OUS Key Opinion Leader

"[BACE inhibitors] are only going to really work at the very earliest part of the disease, so in the symptomatic phase they may not work, just like solanezumab." - OUS Key Opinion Leader

Although DMTs are considered to be the "holy grail" of AD treatments, physicians also expressed the importance of symptomatic treatments. Future treatments will most likely be a mix of drugs, and future trials will involve head-to-head comparisons of drugs in different classes in very early stage AD populations.

"The future of Alzheimer's treatment is 'chemo.' It's going to be a cocktail of drugs; not a single one." - US Key Opinion Leader

"[Drugs in different drug classes] will be used in combination, definitely… Alzheimer's is much more complex than anyone had expected… Four to five mechanistic compounds could be used together in later stages." - OUS Key Opinion Leader

WHAT IS THE FUTURE DIRECTION OF AD DRUG DEVELOPMENT?

The series of trial failures of high-profile AD drugs has cast doubts over the future of AD drug development. However, many factors continue to drive drug development in AD. For instance, an increasing number of predictive biomarkers will promote early diagnosis and the use of pharmacological treatment overall, increasing the demand for new treatments and secondary prevention. Recent changes in the FDA approval process for AD drugs means that the FDA approval no longer requires the demonstration of functional improvement, and only requires improvements in cognitive symptoms in AD patients. Although post-approval studies are likely to be required, the change has lowered a high hurdle to reaching the market, encouraging research efforts in the field.

There are a number of barriers that make drug development in this therapy area a significant challenge. For instance, the recent failures have reiterated the importance of enrolling early stage AD patients, and current evidence points to the fact that the majority of the drugs in development, particularly those targeting Aβ, are not going be effective in symptomatic patients with MCI or AD. With the absence of robust biomarkers that accurately identify patients that will develop AD, enrollment of large numbers of preclinical AD patients in clinical trials is extremely difficult. Moreover, high therapy costs are increasingly becoming scrutinized globally, posing a challenge for manufacturers developing expensive and innovative drugs, such as immunotherapies. However, with the lack of treatment options and many countries seeing rising healthcare costs from aging populations and age-related conditions, such as dementia, payers are likely to make exceptions for AD treatments, if it is given that their efficacy and safety have been demonstrated.

Many interviewed physicians expect prescribing patterns in the AD population to change significantly in the near future. As new drug classes enter the market and DMTs become available, multiple products currently in the late-phase pipeline are expected to be prescribed in combination. Therefore, future clinical trials are likely to focus on understanding the combinatory effect of drugs rather than finding a single cure for AD, as it was initially anticipated by the AD community. In addition, clinical trials will increasingly enroll preclinical individuals as patient identification becomes more robust with improvements in imaging and genetic tests becoming widely accessible, making it easier for patients to enroll themselves into trials. Given the need for AD trials to accurately track and monitor patients over a long duration, future trials are likely to incorporate multiple imaging and CSF/blood-based biomarkers rather than the solely using psychiatric assessment tools as endpoints. Regardless of when the first DMT will become available for AD, AD drug development will continue to evolve as the focus shifts to the early AD population and the use of combination treatment. ◆

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BIOGRAPHY

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WEARABLE INJECTORS

Wearable Drug Delivery Devices: An Attractive Proposal

By: Beth DiLauri, MBA

THE CHANGING DRUG DELIVERY PARADIGM

Recent years have seen groundbreaking advances in pharmaceutical development, with increasingly innovative medicines being brought to market every day. However, the cost and complexity of these novel drugs has intensified the pressure to shift medication administration from traditional settings to more cost-effective alternatives. One such alternative is the patient's own home, where life-altering molecules are now regularly self-administered subcutaneously to treat chronic diseases, such as rheumatoid arthritis, multiple sclerosis, and dyslipidemia among others.

Pharmaceutical companies have worked to develop highly concentrated monoclonal antibodies to improve treatment options for these chronic diseases.[1] At the same time, they are looking to ease the burden on patients by reducing injection frequency and enabling home-based delivery. Although this new paradigm holds tremendous potential, it also brings new challenges in drug delivery, which require innovative solutions to effectively address them.

LIMITATIONS OF CONVENTIONAL DELIVERY SYSTEMS

Historically, delivering the small molecule drugs developed to treat conditions such as infection, hypertension, and hyperlipidemia was of little concern, as most of these medicines could be administered orally. Moreover, when the oral route was not an option, most traditional therapies could be easily solubilized and delivered via intravenous (IV), intramuscular (IM), and/or subcutaneous (SC) injection in a relatively small volume of fluid. Recent

FIGURE 1

BD Libertas™, a pre-assembled, fully integrated, mechanical wearable injector designed to deliver 2-10-mL doses of high-viscosity biologics of up to 50 cP.

developments in biotechnology have produced a plethora of protein-based molecules (eg, mAbs) that must be injected to achieve their therapeutic effects. To accommodate the volume limitations of current IM and SC delivery methods, manufacturers must concentrate these mAbs thereby creating an additional challenge of high viscosity formulations.[2]

This trend poses a fundamental problem with two possible solutions, addressed individually or together: 1) increase the injection volume, or 2) increase the injection duration. While these options may be feasible for IV administration, they pose significant impediments to SC delivery, especially when administered by a caregiver or a patient. Physiologically, the SC tissue has a limited physical and absorptive capacity for large volumes (eg, >10mL), and associated injection pressure may lead to drug leakage and injection pain.[3-6] Thus, the clear majority of commercially available delivery devices (ie, prefilled syringes and autoinjectors)

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are designed to administer small drug volumes (1-2 mL) in under 15 seconds. Practically speaking, humans have a finite ability to self-inject over long periods of time with traditional delivery devices, as fatigue and the ability to hold the injection device in place waver.

WEARABLE INJECTORS PRESENT A SOLUTION

Wearable injectors (WIs) are delivery systems that adhere to the body to administer larger volumes (more than 2 mL) of drug subcutaneously over an extended period. For more than a decade, numerous pharmaceutical and medical devices companies have led development efforts to bring WIs to market, including BD Libertas™ large-volume wearable injector (Figure 1). While there is variability amongst products, all WIs provide a reservoir for the medication, a cannula for delivery to the tissue, adhesive to fix the device to the patient's skin, and a drive system to deliver the appropriate drug volume.

WIs effectively address the volume and viscosity challenges of prefilled syringes and autoinjectors, allowing highly concentrated drugs to be diluted into larger volumes and administered over longer periods of time (minutes rather than seconds) without saturating the SC space. Although the potential benefits of these delivery systems are numerous, perhaps the most notable is the ability to self-administer high-volume, high-viscosity drugs in a non-clinical setting (Figure 2).

FIGURE 2

Wearable injectors provide a drug reservoir, cannula, and adhesive to fix the device to the patient's skin.

THE VALUE OF EXPERIENCE

Like all drug delivery devices, a successful WI must be designed to meet the needs of a variety of healthcare stakeholders. Most importantly, the WI must meet patients' needs for simplicity in the non-clinical setting. However, WIs must also meet the pharmaceutical manufacturer's needs for a solution that offers proven, well-integrated components that fit into existing fill/finish processes. This is a significant requirement that demands partners with experience in producing drug delivery devices.

As a leader in delivering high-quality medical devices for more than 100 years, BD can leverage its broad experience to effectively meet these requirements and introduce new drug delivery systems. BD's extensive expertise in medical device development, primary containers, and needles allows for the seamless addition of a WI to any pharmaceutical partner's portfolio.

BD LIBERTAS, THE NEXT GENERATION OF WEARABLE INJECTORS

BD Libertas is a pre-assembled, fully-integrated, mechanical WI designed to deliver 2-10-mL doses of high-viscosity biologics of up to 50 cP. BD Libertas' unique design and interface were informed by extensive preclinical and clinical research, resulting in a WI with minimal steps and little complexity.

"Like all drug delivery devices, a successful WI must be designed to meet the needs of a variety of healthcare stakeholders. Most importantly, the WI must meet patients' needs for simplicity in the non-clinical setting. However, WIs must also meet the pharmaceutical manufacturer's needs for a solution that offers proven, well-integrated components that fit into existing fill/finish processes. This is a significant requirement that demands partners with experience in producing drug delivery devices."

Simplicity in Design

Unlike other WIs, BD Libertas does not require user assembly or filling, significantly reducing the potential for human error and contamination. Devices that require user assembly and filling introduce the potential for dropping (and breaking) the primary container, incorrect assembly, touching aseptic areas, and increasing patient and caregiver confusion. Conversely, BD Libertas comes completely pre-assembled and ready-to-use out of the package, eliminating the greatest source of contamination: human interaction.

This convenient presentation is enabled by a unique fluid transfer valve built into the injector. The valve enables the primary container to be filled, assembled, and packaged in a standard Class 8 manufacturing facility (Figure 3).

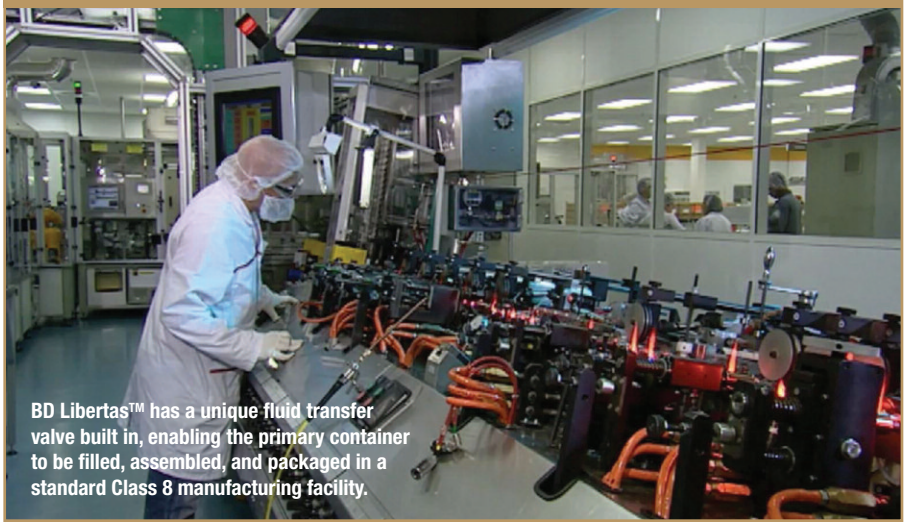
PIONEERING INJECTION RESEARCH

BD has conducted rigorous preclinical and clinical research to ensure effective SC delivery of large-volume injections. The Translational Sciences Center of Excellence at BD Technologies has partnered with BD Pharmaceutical Systems to provide in vivo testing of BD Libertas. This collaboration provides valuable insights to directly impact device design, and offers early information on performance in a living system that is not easily replicated on the bench.

Approximately 40 preclinical studies were conducted to characterize the tissue response to large-volume SC deposition, investigate effects that could influence patient perception of the device, and optimize design and system components. These studies evaluated the device performance across a broad range of injection conditions that pharmaceutical manufacturers may need to deliver their molecules (eg, varying viscosities, flow rates, injection times, or body locations). One extraordinarily valuable aspect of in vivo testing is the ability to develop a model that is a good predictor of human outcomes. With rigorous preclinical testing, BD can quickly gain the information it needs to understand delivery dynamics and device footprint, and optimize device performance before moving on to human testing.

BD has used this extensive preclinical research to inform four in-human clinical studies. Two of these studies were specific to BD Libertas design component optimization, while the remaining were large-vol-

FIGURE 3



BD Libertas™ has a unique fluid transfer valve built in, enabling the primary container to be filled, assembled, and packaged in a standard Class 8 manufacturing facility.

FIGURE 4

BD Libertas™ was designed from the outset with the capacity for smart features, simply by adding a smart module to the core device.

ume injection studies that employed a surrogate system to mimic BD Libertas delivery. Through these clinical studies, BD gained a comprehensive understanding of the large-volume SC injection experience across a variety of injection conditions and valuable insight into patient acceptance and preference. It's important to provide the best possible experience for end users. Optimizing performance early saves time in the development process and gives a much better understanding of users' needs, sooner.

INTEGRATING TRUSTED COMPONENTS

Paired with these novel innovations and capabilities, BD leverages the technologies it already delivers to pharmaceutical manufacturers by the millions every day. The BD Libertas incorporates BD Neopak™ primary container technology and employs the same cannula technology found in BD's world-class needles. BD Libertas was purpose-built to provide a complete solution, anticipating both patient and manufacturer needs.

BENEFITS OF MECHANICAL SYSTEMS

A mechanical drive system, like that found in BD Libertas, provides a robust, industry-tested method of delivering medication. Purely mechanical systems provide reliable and known mechanisms for administration, which may help to reduce risk and increase reliability. In contrast, electromechanical devices typically require pumps, which may introduce technical complexities and unknown sources of error.

Moreover, purely mechanical devices may deliver more comfortable injections compared to electromechanical devices, as they are responsive to tissue back-pressure. As fluid diffuses into the subcutaneous space, pressure in the tissue slowly builds, which may induce pain at the injection site. When this occurs during mechanical delivery, the device responds by naturally slowing the medication delivery toward the end of the injection, reducing the potential for pain. Conversely, electromechanical devices are designed to deliver medication at a constant delivery rate regardless of tissue back-pressure.

A final advantage of purely mechanical devices is simply the absence of electronics from the core device. This is particularly beneficial when it comes to device disposal.

CUSTOMIZATION OPTIONS

BD offers the ability to adapt several aspects of the BD Libertas device, including the look and feel and injection volume, while keeping the core footprint standardized. The WI will be available in two volume formats, 2-5 mL and 5-10 mL, both housed within a similar device design.

BD Libertas' design features customizable outer-facing components, enabling further flexibility without impacting the functionality of the device. For example, grip and button colors can be changed to reflect branding. The device's outer cover can also be modified with components that contain enhanced functionality. In this way, any BD Libertas device can be easily modified or upgraded as needed, without any changes to the core device module.

FLEXIBILITY TO BECOME "SMART"

The BD Libertas design is future-proofed to meet evolving industry trends. More developers are looking to enhance the injection experience by incorporating "smart" features and connecting with the digital health ecosystem (Figure 4). Although a limited number of commercially available drug delivery devices currently have smart features, connected devices are poised to become the norm throughout the next 5 to 10 years.[7]

BD believes that smart devices should encompass both local and global connectivity: local, in that a smart device should help facilitate better interactions with indi-

vidual users, and global, in that the device should enable communication with others about its state and usage. BD has taken this approach in the development of BD Libertas, while also recognizing that not every situation requires the same degree of connectivity.

BD Libertas was designed from the outset with the capacity for smart features, simply by adding a smart module to the core device. In this way, one platform can accommodate both local and global connectivity for the same molecule or across molecules within one customer. BD Libertas truly offers a platform solution for pharmaceutical companies

SUMMARY

Wearable injectors present a robust solution to the challenge of delivering SC injections of increasing dosing volumes and viscosities in non-clinical settings. Introducing robust, innovative technologies will allow more patients to enjoy the convenience of injecting at home. In addition, the ability to accommodate new formulations with higher volume and/or viscosity will enable less-frequent injections, improve the patient experience, and potentially increase adherence to therapies.

However, bringing new injection technologies to market introduces complexities that pharmaceutical companies must consider as they select the right wearable injector platform for their portfolio. Experience in providing prefillable injection technologies, delivering well-integrated primary container and device systems, and working with partners who understand the intricacies of delivering drugs into the subcutaneous space all help to increase peace-of-mind for pharmaceutical companies in bringing combination products to market.

BD Libertas represents the newest addition to BD's platform of integrated device components to support the development of combination products to enable a variety of options for delivering self-administered biologics.

BD Liberta^{sTM} is a product in development; some statements made are subject to a variety of risks and uncertainties.

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BIOGRAPHY

Beth DiLauri is Director, Strategic Marketing at BD Medical – Pharmaceutical Systems, responsible for developing portfolio strategies and leading commercialization for self-injection devices with the Pharmaceutical Systems business. She has dedicated her 18-year career at BD to developing and executing portfolio strategies based on deep market and customer insights, across multiple segments of the healthcare industry, including pharma/biotech, medical devices, diagnostics, and healthcare IT. Prior to BD, she was responsible for business development at Transcend Therapeutics, a venture-backed development-stage pharmaceutical company, from inception through its Initial Public Offering on the NASDAQ in 1997. She earned her MBA from the Tuck School of Business at Dartmouth College (Hanover, NH, US), and Bachelors' degree in Psychology from Boston College (MA, US).

ANTIBODY DRUG CONJUGATES

Expansion of Approved Indications Backs 25% Increase in Global Market

By: Laurie L. Sullivan and Shalini Shahani Dewan, MS

INTRODUCTION

ADCs combine the extraordinary affinity and specificity of monoclonal antibodies with the anticancer potential of payloads. An ADC consists of a cytotoxin linked to a monoclonal antibody, which delivers the cytotoxic payload to specific cancer cells. Once inside the targeted cell, the cytotoxin is released to kill the cancer. Continuous efforts to improve the therapeutic potential of biologics and to develop novel efficacious drugs — either by modification or derivatization — led to the development of ADCs. BCC Research found that growth potential for the ADC market remains promising.

Although the design and synthesis of a fully functional and effective ADC is very challenging, there are now more than 50 ADCs in clinical trials. Anticipated revenues by 2021 reflect the expected approval of ADCs directed toward leukemia and ovarian cancer. With their advantages over conventional chemotherapies, which damage normal tissue, ADCs form a promising market. Technological advancements, the rising incidence of cancer, and an increasing demand for biologic therapies are all factors driving growth in the global ADC market.

Much of this growth is expected to result from additional approved indications for the two ADCs already on the market. These are Adcetris (brentuximab vedotin, marketed by Seattle Genetics Inc. and Takeda Pharmaceutical Co. Ltd.) and Kadcyla (ado-trastuzumab emtansine, marketed by Genentech Inc., a member of the Roche Group). Adcetris was approved in 2011 for relapsed Hodgkin lymphoma and relapsed anaplastic large-cell lymphoma, and Kadcyla was approved in 2013 for HER2 (human epidermal growth factor receptor 2)-expressing breast cancer. By 2021, ADCs for the treatment of breast cancer will represent a market share of 47.1%.

With just two approved drugs, the global ADC market was worth approximately $1.3 billion in 2016. At a 5-year compound annual growth rate (CAGR) of 25.5%, it is predicted to attain $4.2 billion by 2021. By region, North America is the largest market, valued at $588.6 million in 2016. North America is also the fastest-growing market and is forecast to total nearly $2 billion by 2021 at a CAGR of 27.2%. The ADC market in Europe, which reached $395 million in 2016, is expected to be worth close to $1.2 billion by 2021, reflecting a 5-year CAGR of

TABLE 1

Summary Table:
Global Market for Antibody Drug Conjugates, by Region, Through 2021
($ Millions)

Region	2014	2015	2016	2021	CAGR% 2016–2021
North America	463.8	538.6	588.6	1,963.4	27.2
Europe	219.6	379.5	395.0	1,160.9	24.1
Asia-Pacific	152.8	214.7	244.5	733.6	24.6
Emerging markets	80.5	106.3	113.7	312.0	22.4
Total	916.7	1,239.1	1,341.8	4,169.9	25.5

Source: BCC Research

24.1%. Improving economic conditions, a demand for better healthcare facilities, and increasing R&D activities will support growth in the Asia-Pacific region (24.6%).

The market for ADCs is analyzed broadly according to the following categories: target antigen, payload, monoclonal antibody, linker, breast cancer, lymphoma, and other cancers.

TARGET ANTIGENS

Choice of the appropriate target antigen is a critical parameter that affects the efficacy, therapeutic window, and toxicity profile of ADCs. It is crucial that antigens have high selectivity for the tumor cell to limit toxicity and off-target effects. Based on antigen, the market for ADCs is evaluated according to the following targets: CD30, HER2, and other key antigens for ADC development that include CD19, CD22, CD25, CD33, CD56, CD74, and LIV1. The global market for ADCs targeting other such antigens is expected to reach $1.2 billion by 2021.

CD30, the target of Adcetris, is the characteristic marker of classical Hodgkin lymphoma, anaplastic large-cell lymphoma, and embryonal-cell carcinoma. Its restricted expression on normal cells makes CD30 an attractive candidate for targeted therapy. Adcetris is being evaluated broadly in more than 45 ongoing clinical trials. The global market for CD30-targeting ADCs is poised to reach $1 billion by 2021, increasing at a CAGR of 14.9%.

HER2 appears on the surface of some breast cancer cells and is also implicated in ovarian cancer. The increasing incidence of breast cancer is one of the major factors affecting growth of the market for HER2-targeting ADCs. Kadcyla, which targets the HER2 antigen, is being evaluated in seven Phase III clinical trials, as well as in earlier-stage trials. The market for HER2-targeting ADCs was valued at approximately $822.6 million in 2016.

PAYLOADS

A cytotoxin, often called a payload, is designed to induce target cell death when internalized and released. Based on mode of action, payloads fall into three categories: antimitotic, DNA interacting, and transcription inhibitors. Antimitotic payloads include maytansinoids and auristatins. DM1 and DM4 are the most widely used maytansinoids in ADC clinical trials. Monomethyl auristatin-E and monomethyl auristatin-F are important members of auristatins. Kadcyla and Adcetris both contain antimitotic payloads, DM1 and monomethyl auristatin-E, respectively.

Antimitotic and DNA interacting are the two classes of payloads that are most widely used to design ADCs. When stratified by payload, antimitotic is the leading segment in the global ADC market. DNA interacting payloads include calicheamicin, CC-1065 analogs, and duocarmycins. The segment for ADCs with DNA interacting payloads is expected to reach $983.7 million by 2021. Transcription-inhibiting agents include amatoxins, which are small bicyclic peptides that bind to RNA polymerase II and lead to cell apoptosis. Research is underway to understand the use of amatoxins as ADC payloads. Transcription-inhibiting payloads are still in the preclinical phase of development.

MONOCLONAL ANTIBODIES

A monoclonal antibody that is highly selective for a tumor-associated antigen with restricted or no expression on healthy cells is an essential component of an ADC. To maximize efficacy, the antibody should target a well-characterized antigen with high expression at the tumor site and low expression on normal tissue. Based on type of antibody, ADCs can be categorized into those containing a murine, chimeric, humanized, or human monoclonal antibody. Although early ADCs used murine monoclonal antibodies, their immunogenicity has restricted their use in ADC development. Murine monoclonal antibodies have been replaced with chimeric antibodies that have a human constant region and a murine variable region.

Kadcyla and Adcetris are both chimeric antibody-containing ADCs. Expected regulatory approvals for extended indications will further increase the sales of chimeric antibody-containing ADCs during the forecast period. This segment of the market could reach $1 billion by 2021 at a CAGR of 14.9%. However, most ADCs that are currently in use or in clinical development use either humanized or fully human antibodies. Humanized antibody-containing ADCs led the market in 2015 with $770.2 million in sales and are expected to grow at a CAGR of 30.6% through 2021. ADCs with human antibodies are still under development.

LINKERS

Linkers, which enable covalent attachment of the cytotoxic agent to the monoclonal antibody, play an important role in development of safe and effective ADCs.

"Despite the high cost of ADCs, the market is growing steadily. There are myriad factors fueling the industry. For example, manufacturers of branded drugs dread patent expiration, which opens the door to low-cost generic versions that compete with their product. Once that profit is eroded by a generic, the company must make up for the loss of sales through a new or existing product. ADCs are considered attractive because, in most cases, they include an already-marketed drug. Moreover, the chemical complexity of an ADC makes its reproducibility a difficult task for generic manufacturers. In this manner, ADCs provide added patent and profit protection to manufacturers."

The majority of ADCs in clinical development use a limited number of chemical linkers. The mechanism of drug release is an important consideration in linker selection. Cleavable linkers are mostly cleaved from the payload in endosomes or lysosomal compartments via a variety of mechanisms, including acidic degradation, protease cleavage by cathepsin B, and thiol-disulfide exchange reactions. Conversely, non-cleavable linkers require complete lysosomal proteolytic degradation of the antibody, generating a toxic payload with charged lysines or cysteines.

Based on type of linker, the market for ADCs is analyzed by those with cleavable or non-cleavable linkers. Kadcyla belongs to the non-cleavable and Adcetris to the cleavable linker category. Most of the ADCs in development have been designed using cleavable linkers. ADCs with cleavable linkers comprised approximately 62% of the global ADC market in 2015. ADCs with non-cleavable linkers had $519.2 million in 2016 sales. The market for ADCs with cleavable linkers is anticipated to grow at a CAGR of 30.6% from 2016 to 2021, while the segment of ADCs with non-cleavable linkers is expected to increase at a CAGR of only half that (14.9%).

BREAST CANCER

Breast cancer is the most common cancer in the world. According to the American Cancer Society, approximately 14% of breast cancers overexpress the HER2 protein. The discovery of the role of HER2 in breast cancer and consequent development of HER2-targeted therapies has dramatically improved clinical outcomes for women with both early stage and advanced HER2-positive breast cancer. Breast cancer held 61.3% of the global ADC market in 2016. With its one approved ADC (Kadcyla), breast cancer was the largest revenue-generating category by type of malignancy.

The efficacy of Kadcyla in treating metastatic disease is well recognized, and its use in early settings is anticipated. Its high efficacy and lack of side effects have made Kadcyla a successful therapy for HER2-positive breast cancer. Kadcyla is actively being evaluated in combination with other drugs to treat early stage and metastatic breast cancer. Apart from the further investigative studies of Kadcyla, there are several ADCs for breast cancer in development by other companies. The market for ADCs targeted against breast cancer was valued at $822.6 million in 2016 and is expected to grow at a CAGR of 19%.

LYMPHOMA

Lymphoma is the most common blood cancer. The two main forms are Hodgkin and non-Hodgkin lymphoma. The CD30 antigen, the target of Adcetris, is expressed by both these types of lymphoma. There are also other lymphomas that express the CD30 antigen on the surface of malignant cells. Adcetris, which is expected to undergo high double-digit growth, is going to be very effective in these histologic types, which are the subject of further investigations.

The market segment for lymphoma ADCs is expected to reach $1 billion by the end of 2021. Lymphoma held 38.7% of the global ADC market in 2016. The North American market for this category of ADCs is expected to grow at a CAGR of 18.2%. Projections are made on the basis of anticipated FDA approvals for Adcetris' additional indications. The high incidence of non-Hodgkin lymphoma is another factor driving growth of the market. The European market accounted for $55.8 million in 2016 sales. ADCs to treat

lymphoma in this geographic region are expected to increase at a CAGR 15.6% through 2021.

OTHER TYPES OF CANCER

ADCs to treat other malignancies such as ovarian cancer and acute myeloid leukemia are in various phases of development. All types of cancer except for breast cancer and lymphoma are aggregated in this segment. The global market for ADCs to treat these other cancers is expected to reach $1.2 billion by the end of 2021. Among geographies, North America is expected to account for the highest sales, which will mainly be driven by the expected FDA approval of several ADCs in the next few years.

ANALYSIS OF MARKET OPPORTUNITIES

Despite the high cost of ADCs, the market is growing steadily. There are myriad factors fueling the industry. For example, manufacturers of branded drugs dread patent expiration, which opens the door to low-cost generic versions that compete with their product. Once that profit is eroded by a generic, the company must make up for the loss of sales through a new or existing product. ADCs are considered attractive because, in most cases, they include an already-marketed drug. Moreover, the chemical complexity of an ADC makes its reproducibility a difficult task for generic manufacturers. In this manner, ADCs provide added patent and profit protection to manufacturers.

The targeted nature of ADCs has prompted the development of new forms of chemotherapeutics that are too potent to be used systemically, for example, maytansinoids. These compounds are highly potent, antimitotic agents. The cytotoxic agent maytansine was evaluated as a single agent in various types of tumors, but dose-limiting toxicities resulted in the discontinuation of all clinical trials. The conjugation of maytansinoids (specifically DM1 and DM4) to antibodies has significantly decreased the systemic toxicity reported in patients. Kadcyla is an example of an ADC that uses DM1.

Because of their specificity, biologics (especially monoclonal antibodies) have gained a lot of importance as a targeted therapy. The success of Kadcyla and Adcetris (and development of biologics in general) has given investors confidence in the field and encouraged researchers to focus on improving ADC designs. The number of ADCs in clinical development has increased from 33 in 2013 to roughly 60 at the end of 2016. Today, innovative ADC development continues as scientists work on stable linker technologies, more potent payloads, and better target selection.

Naturally, the upside of ADC development is accompanied by challenges. For one thing, ADC manufacturing facilities require high capital investment and extensive specialized training of operators, driving a trend toward the use of mostly contract manufacturers for ADCs. Only a few contract manufacturing organizations have the capability to perform all of the different steps required in the manufacture of ADCs. Thus, one key strategy is collaboration among contract manufacturers to create a one-stop shop for ADC developers.

Also, because developing an ADC is a complex process (which is considered a benefit in the context of generic competition), it makes them risky to produce and test. Careful patient selection is thus another requirement. To deliver the most clinical benefit, ADCs must be used with companion diagnostics to determine if a patient's form of cancer has the target antigen for which the drug was designed. Targets must also be selected carefully to minimize off-target toxicities. Ultimately, challenges in ADC development are trumped by the vast rewards associated with their use for treatment of cancer, resulting in a remarkable market gain of $3 billion over the next 5 years. ◆

This article is based on the following market analysis report published by BCC Research: Antibody Drug Conjugates: Technologies and Global Markets (PHM161B) by Shalini Shahani Dewan.

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Shalini S. Dewan earned her MS in Pharmaceutical Chemistry and has more than 14 years of industry experience. She was awarded a Gold Medal by the Prime Minister of India for her work and has worked with top companies in India and in the US. Some of her other reports for BCC Research include: Global Markets and Technologies for Advanced Drug Delivery Systems, Orthopedic Drugs, Implants and Devices and Global Markets for Reagents for Chromatography.

THERAPEUTIC FOCUS

Applying the HIV Treatment Model to Hepatitis B – Can a Cocktail Provide a Cure?

By: James Sapirstein, RPh

INTRODUCTION

In the ongoing search for a cure to hepatitis B, experts now believe that combining different drugs into a single regimen can work together against HBV and will be the most likely way to achieve a cure. Early trial results using this approach have been promising, and researchers are now turning up the heat in a race to find the right treatment combination.

Hepatitis B is an infectious disease that is caused by the hepatitis B virus (HBV). Affecting the liver and occurring in both acute and chronic modalities, patients who test positive for HBeAg, an HBV surface protein antigen, are said to be chronic and are at risk of developing liver disease if they test positive for more than 6 months.

According to the Hepatitis B Foundation, a national nonprofit organization focused on improving the quality of life and finding a cure for those affected by hepatitis B worldwide, the disease is the most common serious health threat in the world. It is considered up to 100 times more infectious than the human immunodeficiency virus (HIV) and is the primary cause of liver cancer, the second-leading cause of cancer deaths globally.

CHRONIC HEPATITIS B OVERVIEW

A 2016 report released by the National Academy of Sciences, Engineering and Medicine (NASEM) states that hepatitis B and C account for 78% of the world's hepatocellular carcinoma cases and more than half of all fatal cirrhosis cases every year. Moreover, it surpassed HIV and AIDS to become the seventh leading cause of death in the world as recent as 2013.

The virus is transmitted by exposure to infectious blood or bodily fluid, and health officials estimate that 2 billion people have been infected with HBV, and an additional 10 to 20 million people become newly infected each year. Of these, an estimated 1 million people die each year from hepatitis B and related complications, such as liver cancer, according to the report. While Hep B is preventable by vaccination, once infected, there is no cure.

With limited efficacy of treatments for liver cancer and low survival rates, treatment targeting suppression of HBV replication before these complications arise is extremely important to increase longevity.

But there is some good news on the horizon. The NASEM report notes that the elimination of hepatitis B and C is now feasible due to development of new technologies.

FINANCIAL IMPACT

With such widespread infections, the economic burden to treat HBV runs in the hundreds of millions of dollars, based on a 2015 report from the National Institutes of Health.

The total annual cost for the active population of chronic hepatitis B patients and for those receiving treatment at various disease stages is estimated to be $450 million and $226 million, respectively, of which with 64% and 70% are allocated to direct costs, respectively, and 36% and 30% to indirect costs, respectively. It is worth noting that the dollars spent on drugs encompasses the largest proportion of the direct medical cost for all stages of the disease.

THE HIV MODEL

Knowing what we now know about other viral diseases, researchers believe that a cure for hepatitis B may be possible through the full eradication of the virus from the body (similar to hepatitis C) or what is known as a "functional cure," whereby viral levels are minimal, and any negative effects are eliminated with continuous therapy by combining drugs with complementary mechanisms of action. If the latter sounds familiar, it's because this approach is the breakthrough that transformed HIV from a certain death sentence to a manageable disease.

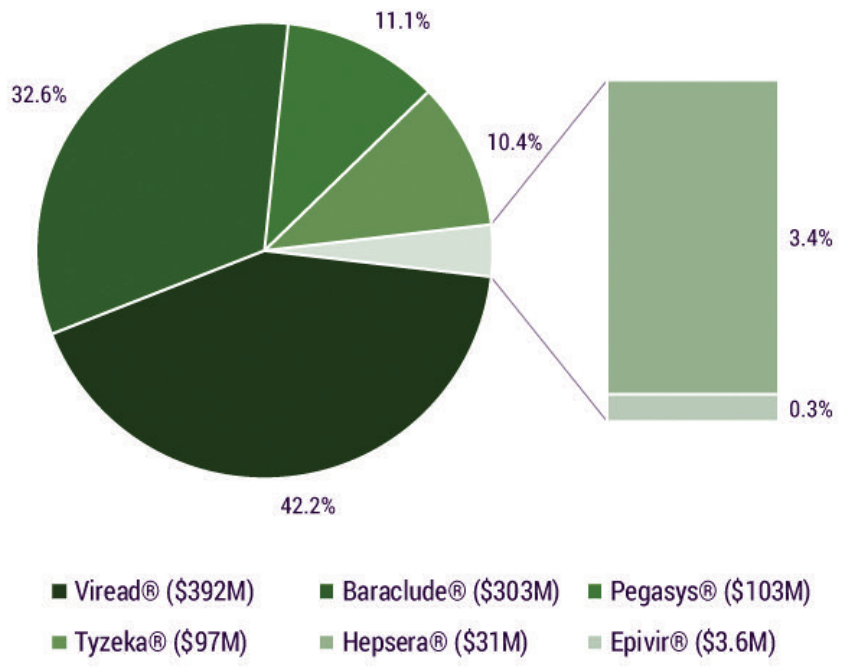
While still considered by the medical community to be one of the largest pandemics in the world, treatment of HIV has come a long way in a relatively short period of time. The earliest confirmed case of HIV in the US was in 1968, suggesting that HIV and AIDS (acquired immunodeficiency syndrome caused by HIV) was present in the US before 1966.

What we know is that hepatitis B isn't a new disease. Researchers recently published findings in a science journal announcing they successfully reconstructed genomes from Stone Age and Medieval European strains of the hepatitis B virus. The recovery of the ancient virus' DNA indicated that hepatitis B was circulating in Europe at least 7,000 years ago. Yet today, scientists are continuing to develop treatments and look for a cure.

Comparatively, it was just a year after AIDS was discovered, that researchers found HIV to be its cause and that the spread of the disease was due to people not knowing that they were infected with the deadly virus, much like it is today with hepatitis. Just two years later, multidrug therapies became widely available, and death rates began to decline. Highly active antiretroviral therapy (HAART), like Combivir, became the new treatment standard and saw the death rate decline by nearly 47%.

Today, there are more than 20 different options available, and the US FDA continues to clear new HIV medical products. And while not totally eradicated, a 2017 study has indicated that persons living with HIV who are being treated with antiretroviral therapy can reduce the virus to undectable levels in the blood that cannot transmit HIV to partners during sex. This brings us to the rationale that the same approach to HIV could work for hepatitis B.

FIGURE 1



US Sales of Approved HBV Drugs (2014)
Compared to therapies for other diseases, only eight have been cleared by the US FDA to treat chronic HBV. These are the leading branded products currently in use based on most recent data (2014).

THE HBV TREATMENT OPPORTUNITY

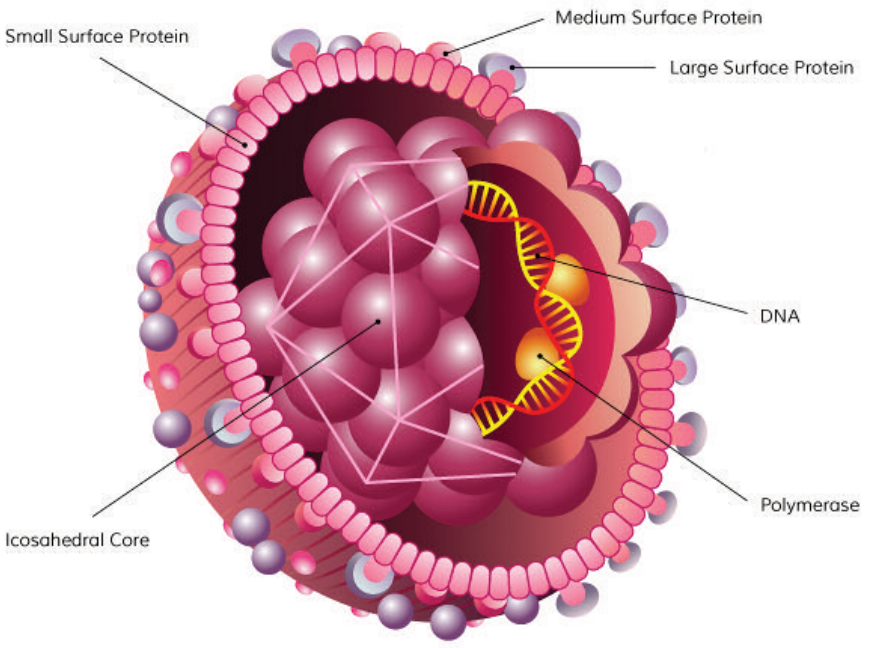
Currently, there are eight FDA-cleared drugs for the treatment of chronic HBV, including interferon-alpha, pegylated interferon-alpha, lamivudine, entecavir, telbivudine, adefovir dipivoxil, tenofovir alefanemide, and tenofovir disporoxil fumarate.

Despite these discoveries, a critical limitation of current therapies is the inability to achieve control of the infection in the vast majority of patients without lifelong treatment. This limited antiviral efficacy of currently approved HBV treatments highlights the need for new therapeutic tools for treating chronic HBV and underscores the need for combination therapy with new classes of agents.

Lamivudine, for example, often results in resistance development, with a 20% chance after 1 year and 70% chance after 2 years. Adefovir, on the other hand, has a much lower rate of resistance development, but has a lower level of potency against HBV.

Various combinations of treatment

FIGURE 2



Hepatitis B Virus
The complex nature of the hepatitis B virus requires new strategies to attack the virus on multiple fronts. While singular-drug therapies may help keep the disease at bay, they do not provide a cure. In the ongoing search for a cure to hepatitis B, experts now believe that combining different drugs into a single regimen can work together against HBV and will be the most likely way to achieve a cure.

have respective advantages and disadvantages, with none being ideal. Nucleoside analog (NA) therapy has advantages over interferon (IFN) therapy, including fewer side effects and easier administration. However, IFN therapy has the advantage of decreased frequency of resistance, and higher rates of HBeAg loss, but also disadvantages of high cost, limited patient response, and administration by injection with frequent side effects.

The drive to find meaningful combination therapy for the treatment of chronic HBV infection stems from the generally accepted principle that a functional cure should address the following:

- Reduction of HBV DNA
- Reduction in the production of viral proteins, including both s- and e-Antigens and protein X
- Reduction/elimination of cccDNA
- Stimulation of the immune response

Exemplifying this strategy is ContraVir Pharmaceuticals, a small biopharmaceutical company that is developing two novel anti-HBV compounds with complementary mechanisms of action.

BLAZING THE TRAIL OF HBV COMBINATION THERAPY

ContraVir's HBV pipeline consists of two drug technologies. The first, tenofovir exalidex (or TXL™) is the prodrug of a well-established anti-HBV nucleotide analog, tenofovir, marketed by Gilead as Viread®, which has been primarily developed to reduce HBV DNA.

The second, CRV431, is a cyclophilin inhibitor with a unique chemical structure that allows the cyclophilin inhibitor to have a wide therapeutic index; in other words, a drug that is highly potent against HBV while providing the potential for minimal toxicities.

The mechanisms of action of TXL™ and CRV431 are distinct and complementary to each other, inhibiting viral replication at multiple different points in the HBV life cycle. In clinical and preclinical studies, each drug has demonstrated unique properties that represent important advances in the treatment of HBV. However, layering CRV431 on top of TXL™ is a strategy that offers the potential to address this need for a combination therapy to target multiple stages of the HBV life cycle.

TXL™ is an antiviral drug that directly targets replication of the virus. It is designed to deliver high intracellular concentrations of the active antiviral agent of tenofovir. TXL™'s novel structure results in decreased circulating blood levels of tenofovir, lowering systemic exposure, and thereby reducing the potential for renal and bone side effects.

According to the World Health Organization (WHO), the likelihood of developing a chronic hepatitis B infection is highly dependent upon the age when the infection occurs. The WHO reports that 80% to 90% of infants infected during the first year of life develop chronic infections and that 30% to 50% of children infected before the age of 6 develop chronic infections (less than 5% of otherwise healthy adults will develop chronic infection).

Knowing that chronic HBV infection is associated with significant morbidity and mortality if left untreated, the FDA granted Orphan designation for TXL™ for the treatment of Chronic Hepatitis B infection in the pediatric patient population. It is the only HBV treatment granted this designation for this group, and underscores the clinical importance of treating HepB in venerable

chronically affected patients.

A new optimized formulation for TXL™ was recently announced, which will allow for more efficient, predictable, and precise delivery to the liver – where the virus resides. The next trial will characterize the pharmacokinetic profile of the new formulation in HBV patients and will indicate the target dose to be advanced into a Phase 3 registration clinical development program.

CRV431 has shown potential in experimental models to complement current hepatitis B treatments by reducing multiple markers of infection including HBV DNA, HBsAg, HBeAg, binding of HBx, and HBV active uptake by cells. Studies have also demonstrated that CRV431 decreases the progression of fibrosis in an animal model and also reduces both the number and size of liver tumors in a hepatocellular carcinoma (HCC) model. These latter two findings offer the potential to not only reduce the virus, but also minimize the impact of the virus on the downstream development of liver diseases.

Additionally and importantly, CRV431 is composed of a unique chemical structure that is known to be a highly potent "host-targeting" antiviral drug with a high selective index against HBV. The hepatitis B virus relies upon its host allowing the virus to propagate and thrive. An important host protein is called "cyclophilin," and this protein participates in many steps of the HBV life cycle. CRV431 offers the potential to disrupt this important part of the HBV propagation cycle.

The safety and antiviral activity of CRV431 is built on a robust set of clinical data from chemically related cyclophilin inhibitors. Due to its immunosuppressive properties, naturally occurring cyclosporine A has been used for more than 30 years in the field of organ transplant, and cyclophilin inhibitors, such as alisporovir (developed by DebioPharm and acquired by Novartis), have achieved clinical safety and efficacy against hepatitis C virus. CRV431 has undergone extensive medicinal chemistry to shed its immunosuppressive activity and optimize its potency and target selectivity, which significantly increases its therapeutic window for treating hepatitis B.

Finally, pursuant to the acceptance of the Investigational New Drug (IND) application by the FDA and an agreement of an accelerated clinical program for CRV431, ContraVir recently announced the commencement of its Phase 1 in healthy volunteers.

These very significant developments serve to differentiate ContraVir as one of the few companies with two oral anti-HBV assets in clinical development.

SUMMARY

Overall, we believe the HBV market is poised for exceptional growth. As in HIV, it is going to take a combined effort to reduce or eliminate the threat that HBV has on society.

The drive to find meaningful combination therapy for the treatment of chronic HBV infections stems from the generally accepted principal that a functional cure should address the reduction of HBV DNA; reduction in the production of viral proteins, including both s-and e- Antigens and protein X, the reduction or elimination of cccDNA, and stimulation of the immune response.

This is a team effort. Researchers must continue to explore and master the science behind the disease, regulators need to be assured that developed treatments are safe and effective, and payors have to be willing to work with regulators and physicians to keep disease screening and treatment costs manageable so everyone has access to the cure.

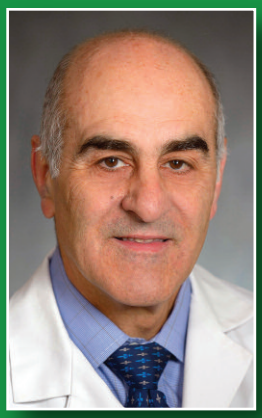
Whatever the outcome, we know we are close to finding a cure for hepatitis B and believe we are at the dawn of a very bright future for HBV patients. It is no longer a question of if or how, but of when. ◆

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

BIOGRAPHY

James Sapirstein is CEO of ContraVir Pharmaceuticals, with more than 30 years of pharmaceutical industry experience. Mr. Sapirstein was the founding CEO of Tobira Therapeutics and also CEO of Alliqua prior to joining Contravir. Prior to Tobira, Mr. Sapirstein was the EVP – Metabolic and Endocrinology at Serono Inc. He served in the Global Marketing group at Gilead, beginning in 2000 where he led and developed the global marketing strategy for its flagship HIV drug, Viread®, and played a key role in the development of the drug combination strategy that resulted in Gilead's acquisition of Triangle's nucleoside portfolio. That acquisition ultimately led to the launch of Truvada, Gilead's multi-billion dollar combination HIV drug. He also spent his first 17 years in the large pharmaceutical company arena, where his last position was the Director of International Infectious Diseases Marketing at Bristol Myers Squibb.

Drug Development
EXECUTIVE



Bill Williams, MD
President & CEO
BriaCell Therapeutics

BriaCell

BriaCell Therapeutics: Recognizing the Power of Targeted Immunotherapies

Dedicated to enhancing the lives of cancer patients who are facing limited therapeutic options, BriaCell Therapeutics Corp's mission has been to develop novel immunotherapies, as the most cutting-edge technology to fight cancer. Immunotherapies have become the forefront of the cancer treatments because they use the body's immune system to destroy the cancer cells, offering higher levels of safety and efficacy than chemotherapy, with less likeliness of recurrence. *Drug Development & Delivery* recently interviewed Dr. William "Bill" Williams, MD, President and CEO, to discuss the value of targeted immunotherapies in the biopharmaceutical industry.

Q: What are the current limitations in the immunotherapy space, and why do you believe an "off-the-shelf" approach is ideal?

A: Immunotherapy takes advantage of the patient's own immune system in fighting cancer. Immune responses all start with an antigen (which is something, usually a protein, recognized by the immune system) encountering an antigen- presenting cell. These antigen-presenting cells take up the antigen and process it. This processing usually involves breaking the antigen up into small pieces (peptides for a protein antigen). These peptide antigens are then bound to molecules called HLA molecules. Structurally, this is like a hot dog (peptide antigen) fitting into a hot dog bun (the HLA molecule). This complex of peptide antigen bound to HLA molecule is then displayed on the surface of the antigen- presenting cell. There it can be recognized by the antigen receptor on a T cell, also known as the T cell receptor. T cells

are white blood cells that coordinate the immune response. Our bodies have billions of T cells with different T cell receptors. When a T cell has a T cell receptor that binds to a peptide antigen – HLA complex, that T cell is stimulated. In the case of a cancer antigen, that T cell would be stimulated to attack the cancer. There are different types of T cells. The major subtypes are CD4+ "Helper" T cells and CD8+ "Killer" T cells. The CD4+ T cells recognize peptide antigens bound to Class II HLA molecules, while the killer T cells recognize peptide antigens bound to Class I HLA molecules.

If T cells recognize a cancer antigen, they should be stimulated to attack the cancer. However, cancers have several strategies to avoid immune attack. One strategy is to shut down the T cells by making a molecule called CTLA4. CTLA4 works to deactivate both helper and killer T cells. This is a so-called immune checkpoint, as during normal immune responses (eg, when fighting an infection), CTLA4 is expressed late in the immune response to cool off the immune system after it's work is done fighting off the infection. Cancer cells will sometimes express CTLA4, or stimulate its expression on other cells, to stop the immune system from attacking the cancer. Yervoy (ipilimumab) works by binding to CTLA4 and preventing it from shutting down the immune response. Another mechanism is for the cancer to express another checkpoint, called PD-L1 or PD-L2. These molecules can be expressed on the cancer cell and can bind to a molecule on CD8+ killer T cells called PD-1. This will shut off the killer T cells. This immune checkpoint has been the subject of great interest with several drugs currently available that bind either to PD-1, such as Keytruda (pembrolizumab) and Opdivo (nivolumab) or to PD-L1, such as Tecentriq (atezolizumab), Bavencio (avelumab), and Imfinzi (durvalumab). These current immunotherapies are known as checkpoint inhibitors. Because they work by releasing suppression of the immune system, they are prone to side effects. Immune checkpoints are typically used to prevent development of autoimmune diseases, where the immune system attacks normal tissues of the body. Because the current checkpoint inhibitors, as well as others in development, do not distinguish cancer-specific immune responses from any other immune response, they can lead to the development of autoimmune diseases. Thus, use of these agents can cause inflammation of the intestines (enterocolitis), liver (hepatitis), skin (dermatitis), nerves (neuropathy), and glandular system (endocrinopathy). This is because checkpoint inhibitors work by taking the "foot off the brakes" of the entire immune system.

Ideally, the immune response should be directed toward the tumor and not the rest of the body. Such a targeted immune response has been attempted using so-called "therapeutic cancer vaccines." However, these have generally not been successful. One exception is a personalized medicine called Provenge (sipuleucel-t). Provenge works by taking antigen-presenting cells from a patient, stimulating them, and charging them with prostate-specific antigen (PSA). These are then given back to the patient where they induce an immune response specific for prostate cancer. Provenge prolongs survival in prostate cancer patients but suffers from the drawback that each dose of the treatment has to be manufactured for each patient. This is time consuming, very costly, and difficult to generalize. Ideally, it would be best to generate a targeted, personalized immune response against the cancer with an agent that is more readily available, or off-the shelf. This would combine the success of the personalized approach with the ease of administration with an off-the-shelf drug. Such an agent, which puts the "foot on the gas" of the immune response, but in a targeted way only against the cancer, should also readily be combined with checkpoint inhibitors, which have a complementary mechanism of action.

Q: How does your signature immunotherapy drug work?

A: Our immunotherapy works by inducing an immune response specific for breast cancer and personalized to the patient. Bria-IMT™ was developed by Dr. Charles Wiseman at Saint Vincent's Medical Center in California. Dr. Wiseman was treating a patient with metastatic breast cancer, and he obtained a piece of her cancer. He took this into the laboratory and developed a cell line called SV-BR-1. He then would take some of the SV-BR-1 cells and irradiate them, so they would not grow and used these to immunize patients with breast cancer against their tumors. He devised a regimen to boost the immune response. This included some low-dose cyclophosphamide to reduce immune suppression and local injections with granulocyte-macrophage colony stimulating factor (GM-CSF) to boost the response. He treated 14 patients with this regimen and had better clinical outcomes than expected. Dr. Wiseman then decided to engineer the cell line to directly express GM-CSF. He dubbed this SV-BR-1-GM, aka, Bria-IMT. He treated an additional 4 patients with irradiated Bria-IMT in conjunction with low dose cyclophosphamide to reduce immune suppression and followed-up with local interferon alpha to help boost the response. They all did well in general, but one patient in particular stood out. She had metastatic breast cancer that had initially responded to chemotherapy but then she relapsed. The cancer had metastasized to the lungs, soft tissues, and bones. After 5

After 5 treatments over 3 months, the cancer had shrunk, and then after a total of 7 treatments over 5 months, the lung and soft tissue metastases had disappeared, the breast tumors had gotten much better, and the bone metastases also improved. At that time, the study only allowed 5 months of treatment, so the treatment stopped. She relapsed several months later, and this included spread of the breast cancer to the brain (brain metastases). She was treated again and responded a second time, including disappearance of the brain metastases. Further analysis showed that she matched with Bria-IMT for HLA type.

HLA molecules were mentioned earlier. These are the molecules that bind antigenic peptides and present them to T cells. HLA molecules are known to be "polymorphic." That means that they are different in different patients but shared by some patients. This is an inherited trait similar to eye color. Eye color can be different in different people, but it is also shared by some people. HLA molecules are like that: they are different in different people, but it is also shared by some people. When people get tissue transplants (like kidney transplants), they are matched for HLA type. So immunologically it makes sense that the patient with the best response matched Bria-IMT at HLA because the same HLA type that is recognized by cancer-fighting T cells on Bria-IMT would also be present on the patient's own cancer. The antigen-HLA complex recognized by T cells on Bria-IMT would stimulate cancer-specific T cells. These would then recognize the same antigen-HLA complex on the patient's own cancer and attack it. This explains why the patient with the HLA match with Bria-IMT had the best clinical response.

BriaCell is using this information to innovate. We are modifying the HLA-type of the SV-BR-1 cell line, so we will be able to match more patients. Currently, the HLA types expressed on Bria-IMT match at one HLA allele to ~50% of the population, and match at two alleles for ~20%. (An allele is a version of a gene. For example, each person has two copies of each gene, one from their mother and one from their father. For eye color, they might have inherited a gene for blue eye color from their mother (the blue eye color allele) and the brown eye color allele from their father. We have determined that with eight different Class I HLA types (or alleles) and seven different Class II HLA alleles, we can single match >99% of the breast cancer population and double match ~90% of the population. BriaCell is developing SV-BR-1 cell lines that will express GM-CSF (as Bria-IMT does) along with interferon-alpha to stimulate the immune response. We will engineer these cells to express 15 different HLA alleles. These cell lines will be pre-manufactured, irradiated, and frozen in a state that will allow them to be shipped directly to clinics where they can be thawed and used to inject patients directly. This will allow us to match the cell line to the patient, providing personalized immunotherapy that is off-the-shelf (Bria-OTS™).

Q: What has earlier proof-of-concept studies shown and current Phase I/IIa data shown?

A: I mentioned some of the early clinical studies earlier. Briefly, Dr. Wiseman treated four patients with the Bria-IMT regimen and had one remarkable responder who matched Bria-IMT at some HLA types. More recently, we treated an additional six patients in 2017. These patients all had very advanced breast cancer. The treatment was safe and well tolerated, and we had an additional remarkable responder. This patient had breast cancer that had spread to the liver and to the lungs. She had 20 different breast cancer metastases in the lungs. She also had failed seven prior rounds of treatment with eight different agents. In spite of this, all 20 of her lung metastases shrank and most completely disappeared with Bria-IMT treatment. She also matched Bria-IMT at two different HLA-types. This is very important confirmation of our HLA-matching hypothesis. This study is ongoing, and more patients are being treated. So far, treatment has been safe and well tolerated. We expect additional data to be available later this year on at least 12 patients.

Q: Why does BriaCell believe combination therapy is key?

A: Combination therapy has shown great promise for immunotherapy for some diseases. This includes combinations of two checkpoint inhibitors, both working by essentially "taking the foot off the brakes" of the immune response. But the side effects of autoimmune disease may also worsen for the combinations. Bria-IMT and Bria-OTS are designed to put the "foot on the gas" of the immune response in a targeted way, just targeting the cancer. So, when combined with checkpoint inhibitors that take the foot off the brakes, this should produce a very potent immune response against the patient's cancer without worsening the autoimmune side effects.

Q: Your team is exploring HLA-typing? What can that offer patients?

A: HLA typing offers the chance to have patients treated with Bria-OTS, which will be personalized and tailored to induce to most potent immune response against the cancer. But the cell lines used will be pre-manufactured and stored in the frozen state, which offers the convenience of an off-the-shelf therapy. Contrast this with the recently developed CAR-T therapy. This therapy requires that patients have white blood cells removed and then manipulated in tissue culture, and then infused back into the patient. This process takes approximately a month, is very expensive, and has to be repeated for each treatment. The same is true for Provenge (mentioned earlier). Or approach circumvents these logistical and cost problems by using cell lines that grow easily in tissue culture at low cost and are pre-manufactured. The HLA typing personalizes the process, so you still get an immune response tailored to the patient.

Q: What is the timeline for your breast cancer drug?

A: Bria-IMT is in Phase IIa testing now and could progress on to a registration study as early as 2020. This would mean filing a licensing application with the FDA in 2022 and marketing approval as early as 2023. These are aggressive timelines but are feasible given the large unmet need in advanced breast cancer and the progress we have made in manufacturing. The Bria-OTS cell lines are being developed with the goal of initiating GMP manufacturing later this year and introducing them into the clinic in 2019. We anticipate ~2 years for Phase I/IIa testing to establish the safety of the new cell lines and preliminary efficacy. We would then negotiate with the FDA the design of a pivotal registration study, which would likely take ~1 year to recruit, 1 year to run, and 6 months to compile the data for filing with the FDA. Assuming accelerated review, Bria-OTS could be approved 6 months later (~2025).

Q: What will your team be doing with checkpoint inhibitors? Protein kinase C Delta?

A: Our team is in conversation with multiple large- and medium-size pharmaceutical companies to perform additional combination studies with other checkpoint inhibitors. This includes approved drugs (Keytruda, Opdivo, Yervoy, Tecentriq, Bavencio, and Imfinzi) as well as other drugs in earlier stages of development. We hope to run additional combination therapy studies, so we can best evaluate the combinations that will have maximal benefit for the patients.

The protein kinase C delta (PKCδ) program is separate from Bria-IMT and Bria-OTS. This program is based on the observation that ~30% of all cancers have mutations in a gene called RAS, and mutated RAS can drive these cancer cells to grow and proliferate. Many pharmaceutical companies have tried to make a RAS inhibitor, but to date, none have been successful. However, cells that are transformed by RAS mutations appear to become "addicted" to PKCδ signaling. This appears to be because PKCδ acts on RAS to prevent it from being broken down and degraded. When PKCδ is inhibited in a RAS-transformed cancer cell, the RAS is degraded, and the cells stop growing and die. BriaCell has licensed PKCδ inhibitors that are small molecule drugs. These are potent and selective inhibitors. They have shown activity against a number of RAS-transformed cancers in pre-clinical studies, including pancreatic, colorectal, lung, and breast cancer as well as melanoma. We are perfecting the drug-like properties of our molecules and hope to introduce them into the clinic within the next 2 years.

Q: How do you stack up to other immunotherapy companies?

A: BriaCell is markedly undervalued compared with other immunotherapy companies at a similar stage of development. BriaCell is in Phase IIa clinical testing, with cutting-edge technology, developing an off-the-shelf approach to personalized immunotherapy. But our valuation is far below other companies at a similar stage of development, and even below the value of many immunotherapy companies that have not yet entered the clinic. BriaCell has an experienced management team, is involved in over 10 drug approvals, and is establishing proof-of-concept for a large number of drugs. This experience will ensure that Bria-IMT, Bria-OTS, and PKCδ inhibitors will be properly developed to reach the finish line. This should benefit a large number of cancer patients as these promising drugs become available. ◆

Technology & Services Showcase

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Technology & Services Showcase

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Technology & Services
SHOWCASE

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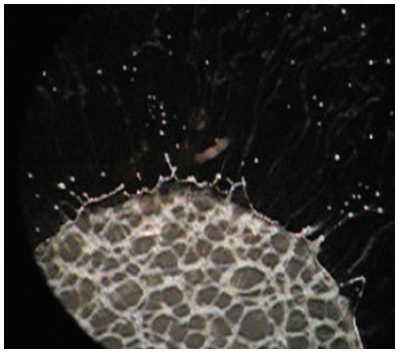

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CLINICAL TRIALS

How to Make Clinical Trials Patient Centric: Five Common Sense Steps

By: Rosamund Round

INTRODUCTION

Too many clinical trials fail because they can't attract or retain enough patients. One recent study of 2,579 clinical trials showed 19% of them had been terminated for failing to recruit patients or for recruiting less than 85% of planned enrollment, seriously compromising the statistical validity of the results.[1] Even trials that recruit enough subjects can flounder if too many of them drop out before the study is complete. For example, on average, one-third to one-half of patients enrolled in randomized controlled trials (RCTs) testing weight loss drugs quit early, within 1 year.[2] One recent study testing a new therapy for patients with chronic pain due to spinal cord injury saw a 76% attrition rate, with only 8 of 46 patients who finished the study.[3]

Statistics like these have inspired pharmaceutical companies to try to make clinical trials more "patient centric" to better accommodate patients' needs and preferences. This includes making it easier for patients to learn about and participate in trials, as well as improving the patient experience, not only to improve retention but to create future advocates for trial participation.

Research suggests the cumulative impact of a relatively modest investment in patient engagement avoids at least one protocol amendment, improves enrollment and adherence. Even more, retention in Phase III can produce a 500-fold increase in expected net present value of the investment.[4] It can also shave up to 18 months off time to market.[5]

Most companies know they need to make trials more patient-friendly, but few have access to the tools and methodologies to transform their protocol design process. Fortunately, thoughtfully applied common sense practices can create better patient experiences and more robust trials.

FIVE STEPS TO OPTIMIZE STUDY PROTOCOLS FOR PATIENTS

To create a patient-centric trial, design optimization should be verified via systematic processes before the trial starts. To test and refine protocols to achieve the right balance between scien-

FIGURE 1

Patient Profile – Understanding the patient as a person

tific rigor (ie, generating sound and comprehensive data to demonstrate safety and efficacy) and feasibility for patients (ie, designing a trial within the logistical and practical reach of the maximum number of people), companies can use the following five tools:

No. 1 - Create an Accurate Profile of the Target Patient

Researchers spend months establishing eligibility criteria for clinical trial participants to ensure a study can answer precise scientific questions. To make a trial patient centric, it's also necessary to dedicate sufficient time to understanding patients' everyday lives and the parameters that affect their participation.

Having a detailed profile of a trial's patient population (and understanding who they are as individuals) can inspire improvements to the protocol that can make the difference between success and failure. Key issues that must be addressed include:

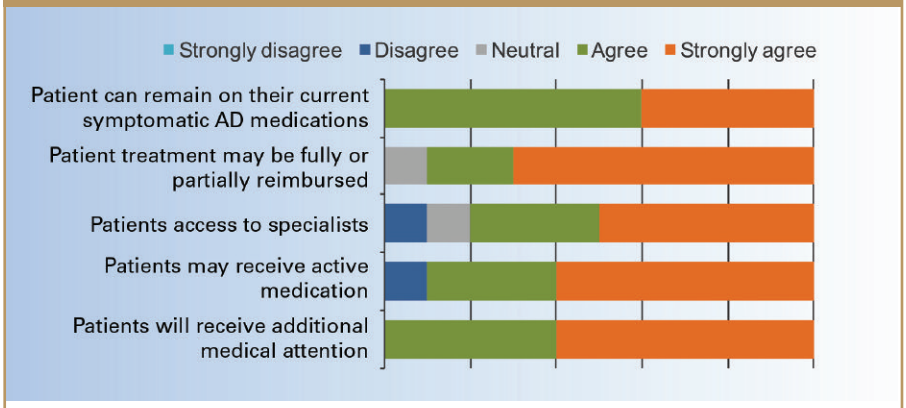
- Demographics of the patients in the study and how that may impact their habits. Are they elderly and may have difficulty leaving home? Are they young adults who can travel easily? Or, are they small children who must be supervised by parents?

- Type of treatment being tested may impact motivation. For example, is it curative or palliative?

- Payment. Will the costs of participating in the trial be reimbursed?

- Real life impact. What is life like with this disease? Do patients have routine, frequent doctor appointments and/or hospitalizations, similar to trial site visits or interventions? Or do they have very few medical interventions, making trial-related testing and procedures more out of the ordinary?

FIGURE 2



Patient Burden Analysis – Leveraging specialist nurse feedback to understand patient visit burden and ways to make participation easier for them.

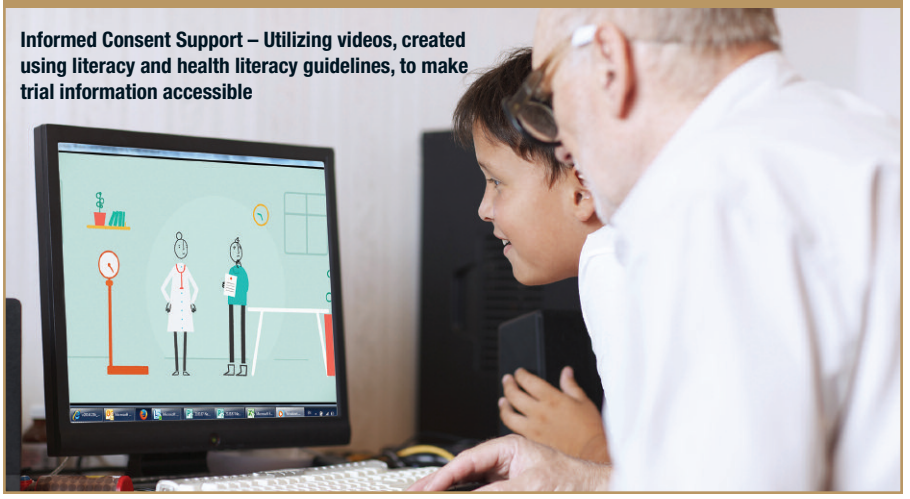
An accurate patient profile is a good starting point when shaping trial design, providing an opportunity to explore what has the biggest impact on participants. For example, if given the option, how would they weigh up a choice between a lower visit burden or fewer invasive procedures? By profiling the patient, we can begin to explore such sensitive areas to create a truly patient-centric approach. We're shifting the discussion from purely answering the scientific question of "Does this patient fit the eligibility criteria?" to "How would the practicalities of study participation impact their decision to join and remain in a trial? And how can we minimize the geographical, financial, and practical barriers to participation?"

No. 2. - Survey Patients & Caregivers for Insights

Pharmaceutical companies can survey patients, caregivers, and nurses/physicians about key aspects of a study to gauge how it may be received. Eliciting such feedback seems like common sense, but incorporating patient and caregiver needs, views, and experience is a relatively new approach in this context — and one that has shown great value.

For example, one company designing a study in young children with severe epilepsy worried that the three 72-hour hospital visits required in the protocol might take too high a toll on very young patients. They surveyed caregivers to find out, on average, how many times in a normal year their children were admitted to the hospital and for how long. The results were surprising. Parents said their children wound up in a hospital about three to five times per year on a routine basis — and that most visits lasted at least 3 days. The company concluded that the trial protocol did not place an undue burden on these already very sick patients and their families as the visit burden was similar to standard of care. Because the required hospital visits were needed to conduct a critical test, the company followed the protocol as planned. But the survey uncovered a different problem: parents reported that caring for their other, healthy children was the biggest challenge of epilepsy-related hospitalizations. To address that, the company explored plans to work with sites to offer flexible visit timing to simplify for parents the process of securing childcare.

FIGURE 3



Informed Consent Support – Utilizing videos, created using literacy and health literacy guidelines, to make trial information accessible

No. 3 - Seek an Unfiltered Reality Check on the Web

There has been an explosion of open online forums, tweets, and blogs where patients share stories about their disease and treatment options. "Listening" to the web through search terms, and dipping into online chatter can give companies unfiltered insight into what really matters to patients. Patient stories capture, often poignantly, what it's like to live with a disease in non-medical terms and may inspire new approaches and ideas.

For example, one company developing a treatment for Crohn's Disease read a number of blogs written by the children of Crohn's sufferers and got a deeper perspective on how frightening the disease can appear to them. Crohn's patients can become alarmingly thin and weak, and their children may worry that their parent will not survive. If their parent is hospitalized, some stay with relatives for extended periods, which can cause fear and upset. The high volume of stories from the children and caregivers of Crohn's patients online indicated that the whole family is highly involved in treatment decisions. Therefore, to optimize recruitment, the company tailored its educational materials to help facilitate a joint decision-making process around trial participation.

In a recent Alzheimer's Disease (AD) study, an analysis of web postings revealed that far more online chatter about AD came from caregivers than from patients. Therefore, an important component of the recruitment and retention strategy was to engage and educate caregivers by explaining the objectives of the study to them and treating them as partners. The web analysis also revealed that AD patient advocacy groups (PAGs) are very active online and are a trusted source of information and support for caregivers and patients. The company thus knew it would need to leverage existing relationships with PAGs, as well as forge new ones, in addition to high online visibility to meet its recruitment goals.

No. 4 - First Quantify, Then Mitigate, the Study Burdens

Most patients have never participated previously in a clinical trial. Although they may know a lot about living with their disease, they are inexperienced in planning clinical research logistics. So, while you can learn a lot from patients, you need to probe further.

Nurse specialists with deep experience at high-volume/high-performing investigative sites are among the most astute judges of the burdens a clinical trial can impose on patients. Their analysis of the potential benefits and challenges of study participation is a valuable resource. Questions they can answer include the following:

- How does the burden of this study compare to the standard of care?
- What could be changed to make it easier for patients?
- How long will each visit last?
- What information will be most useful to support patients in learning about and participating in this study?

Recently, a team of nurse specialists drawn from a network of top research sites helped make a protocol more patient friendly by nixing several planned patient questionnaires. Looking at the number, length, and scope of these questionnaires, the nurses predicted patients would balk at answering so many questions so often during the study. In this case, the solution was to prune some of the trial's exploratory endpoints, which cut down on the number and length of the questionnaires.

However, even experienced clinical staff can misunderstand the issues that worry or, conversely, motivate a patient. For example, in a recent osteoarthritis study, a large majority of experienced nurses who were surveyed about the trial's design said that the inclusion of home nursing visits in a protocol (versus visits at the investigative site only) would have no impact on a patient's willingness to participate in a study. In contrast, a patient survey asking the same question showed patients viewed home visits as a positive

benefit. The survey didn't capture enough data to explain the reasons for this discrepancy, but it is possible the nurses' responses were based on how attractive home visits were from their perspective as caregivers rather than from the perspective of a patient.

No. 5 - Simplify & Standardize Informed Consent

A typical informed consent form is notoriously long and can include a lot of terminology that is unfamiliar and, to most, incomprehensible. Recruitment and retention can be improved by simplifying the informed consent process and making the core document more comprehensible. One way to communicate complex information simply is to break the elements of a study into short (no more than 1 minute) video modules.

For example, a recent trial enrolling 5- to 11-year olds in the United States and South Africa had a complex schedule of events, including two mandatory overnight stays in the hospital. Patients and their parents needed a clear explanation of the trial's procedures and expectations to provide informed consent. So, the pharmaceutical sponsor developed an animated video (translated into the local languages) that explained the study's activities, and showed how the drug worked. By providing the information in this way, parents and children gained a good understanding of what study participation would mean for them. With this tool, enrollment for this trial completed 5 months ahead of schedule with no dropouts.

PATIENT CENTRICITY IS NOT A BUZZWORD

Optimizing a trial protocol for patients is always preferable and, with a bit of care and thought, most often achievable within the normal trial planning timeline. And patient centricity is achieved not in isolation of the doctors and nurses who routinely care for the patients but rather in collaboration with them. Investing care and thought can yield big rewards. It also may prompt positive changes to a protocol, or validate the existing plan. In either case, elevated recruitment and retention levels, and happier trial participants, is worth the investment.◆

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BIOGRAPHY

Rosamund Round is PAREXEL's Patient Centricity Lead and spends her time devoted to simplifying the patient journey in clinical trials. Focused on the reduction of geographical, financial, and practical barriers to study participation, she is excited by the industry shift toward a truly patient-centric approach. Her first job in an oncology clinic at Massachusetts General Hospital sparked her passion for putting patients at the center of clinical research planning and implementation. Subsequent roles in patient recruitment in both the pharma and CRO industries have enabled her to innovate and explore better ways to communicate with patients. This includes addressing literacy and health literacy, exploring technological advancements, and constantly scanning the environment to help generate new ideas to make clinical trial participation more accessible and convenient for patients.

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