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Drug Development & Delivery®

June 2016 Vol 16 No 5 www.drug-dev.com

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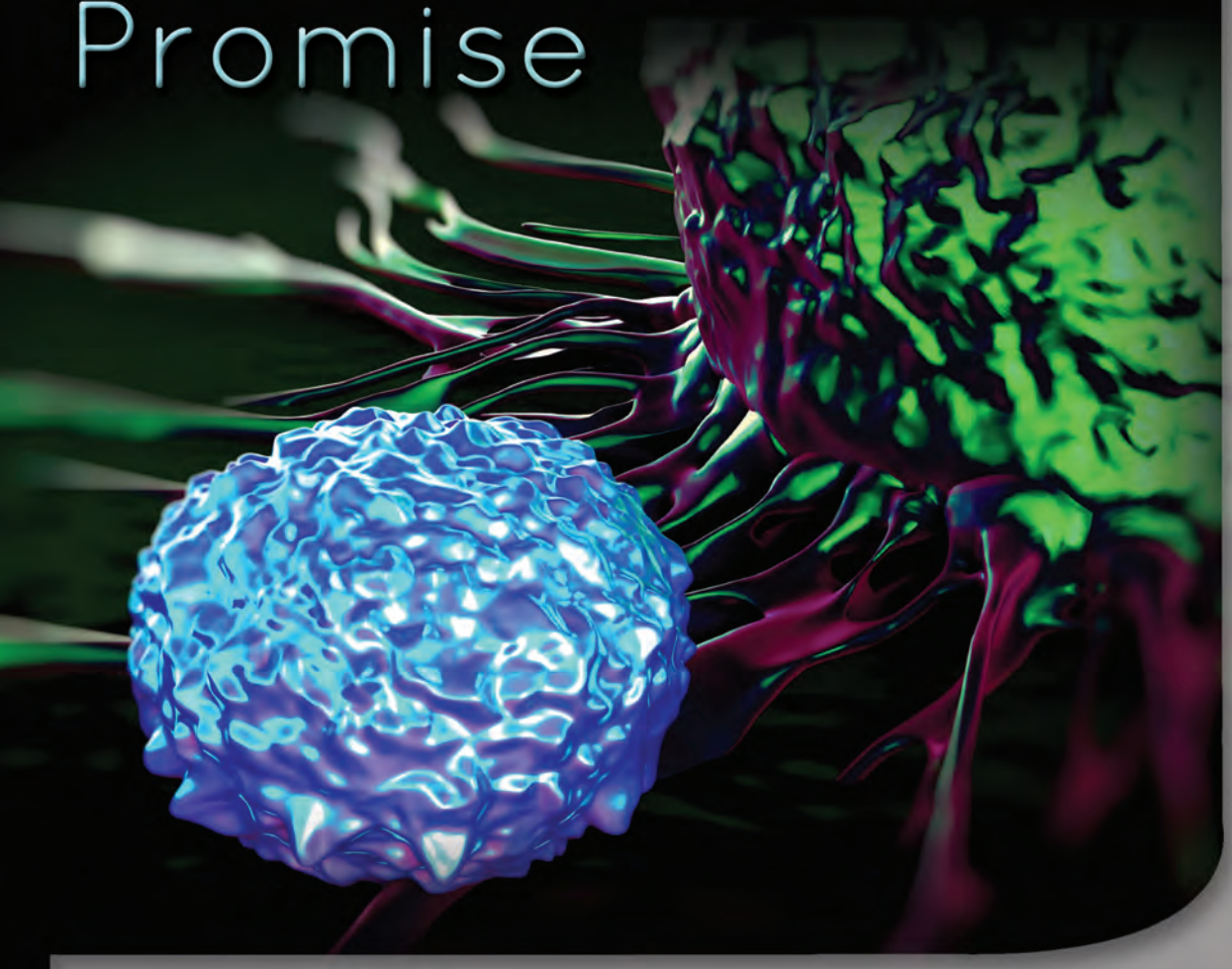

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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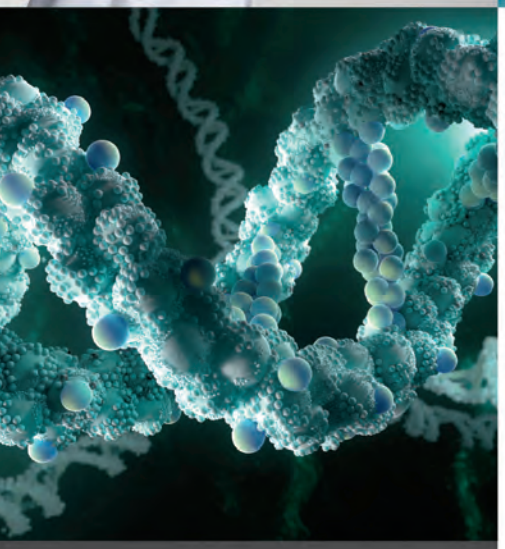

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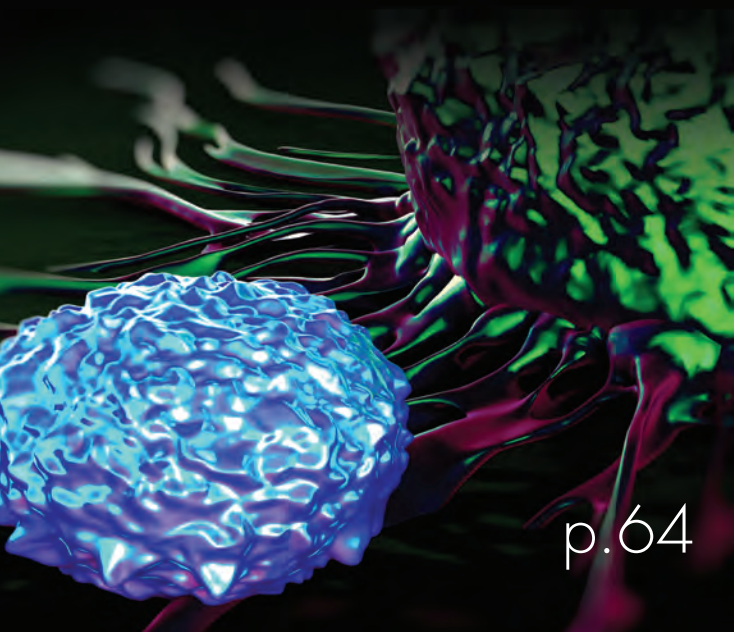

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New Company Created to Develop Novel Technology to Treat Diabetes

The Cell and Gene Therapy Catapult (CGT) and University of Aberdeen, UK, recently announced the creation of Islexa, a new company developing a novel technology to produce laboratory grown islets, the organoids responsible for insulin production.

The technology could bring the option of an islet transplant to thousands more patients with type I diabetes. Currently in the UK, only 30 to 50 patients with hypoglycaemic unawareness can receive an islet transplant each year due to the low availability of suitable donor organs and the difficulty involved in extracting the islets.

Islexa technology works by reprogramming donated pancreatic tissue into fully functional islets that will significantly increase the number of patients who can receive the treatment. An islet transplant can give patients effective, long-term glucose control without the need of insulin administration.

"This is a really exciting technology that has the potential to bring life-changing benefits to these diabetic patients," said Keith Thompson, CEO of the Cell and Gene Therapy Catapult and an Islexa Director. "We are delighted to be forming Islexa with the partners we've worked with so far on this project. The collaboration has already delivered promising results, and the formation of Islexa will accelerate the development of these lab-grown islets and ultimately get this potential treatment to thousands of patients."

"The technology is based on converting pancreatic tissue into functional islets," added Professor Kevin Docherty, University of Aberdeen. "This has an advantage over the use of stem cells as source material, since at the moment they generate only the insulin-producing beta cells. Islets are organoids that produce multiple hormones, including insulin, and donated islets are already effectively treating severe cases of type 1 diabetes. Having a hugely expanded supply of lab grown islets will enable us to significantly extend this established clinical treatment."

The creation of Islexa follows successful results in preclinical studies on the technology and the company will hold future IP rights of the islet technology. The company will initially continue to focus on further preclinical development of the protocol for reprogramming the pancreas tissue into functional islets. The next stage is to take the technology into clinical trials in the next few years.

The expansion and reprogramming technology has been developed at the University of Aberdeen as part of activities led by a consortium with the support of the Cell and Gene Therapy Catapult. The consortium partners include University of Aberdeen, the Scottish Islet Transplant Programme, University of Edinburgh, and the Scottish National Blood Transfusion Service (SNBTS). The consortium partners bring unique expertise in clinical practice and manufacture, and will continue to work closely with Islexa during the development programme.

Juniper Pharma Strengthens Topicals Capability

Juniper Pharma Services, a subsidiary of Juniper Pharmaceuticals, Inc., has reinforced its early stage topical and semi-solids capability by investing in a Becomix homogenizer mixer.

The installation and validation of the new equipment extends the company's ability to manufacture creams, ointments, and semi-solids to support clients' clinical trial needs and enables it to efficiently deal with more complex formulations.

Used primarily for the production of topical drug products, the Becomix RW30 model homogenizer gives the contract development and manufacturing organization (CDMO) the scalability to now supply products for Phase III studies.

The move by Juniper Pharma Services to make a significant investment into its topical and semi-solids equipment follows an increase in demand from its clients for development, processing scale-up, and clinical manufacture.

"This addition to our capabilities enables us to develop topical products on a larger scale and to cater for our clients' supply needs from first-in-man studies up to and including Phase III, with a commercially replicable process in place," said Claire Madden-Smith, SVP at Juniper Pharma Services. "We are no stranger to aiding clients with challenging formulations and so the installation of Becomix simply bolsters our ability to support drug development companies that are developing creams, ointments, and semi-solid products, both simple and complex."

With an integrated electronic batch report system in place, the intuitive Becomix is designed to reduce operator input and automate the homogenization process. This is the latest major equipment initiative by the CDMO, which recently announced a substantial investment in its spray-drying capabilities. This followed the strengthening of its early stage capsule filling expertise with the expansion of its Xcelodose powder micro-dosing system at the end of last year.

With a strong track record of helping pharmaceutical companies develop and produce oral and topical drug products for clinical trials, Juniper Pharma Services is able to optimize formulation performance through its science-led approach to projects.

The CDMO's GMP clinical manufacturing capabilities are based at its site in Nottingham and are supported by its materials characterization, analytical, and IP consultancy services.

Juniper Pharma Services Ltd., a wholly owned subsidiary of Juniper Pharmaceuticals, Inc., is a contract development and manufacturing organization (CDMO) that specialises in small molecule formulation development. Its development services extend from pre-formulation and formulation development to clinical trial manufacturing, with specialist capabilities on working with or around the properties of challenging drug molecules. Juniper Pharma Services is also renowned for its expertise and toolkit to analytically resolve some of the toughest issues during development and relating to intellectual property issues. The company's services are dedicated to pharmaceutical, biopharmaceutical, and healthcare companies across the globe.

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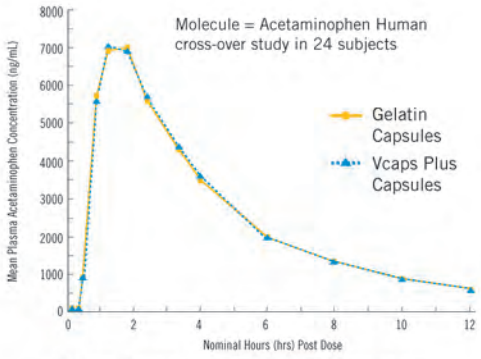

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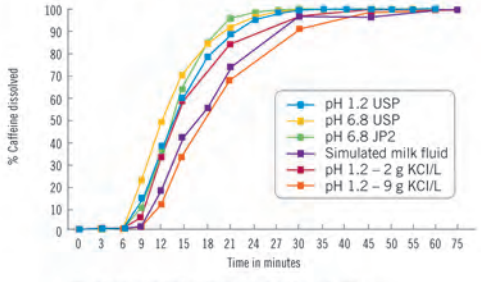

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Lonza CytoSMART Lab Free-Trial Initiative Launched

Any laboratory wanting to experience Lonza's CytoSMART System can now apply to become a Lonza CytoSMART Lab. In this exciting new initiative, Lonza is offering a 4-week free trial of the easy-to-use CytoSMART System that allows researchers to remotely perform live cell monitoring and record time-lapse videos of their cell cultures. Scientists can view their cells without having to open the incubator door - or even visit the lab. Lonza will also feature the chosen laboratory's CytoSMART Project prominently on the company's website, enabling scientists to share their latest research with their peers.

The CytoSMART System can be set up in minutes and is small enough to easily fit inside most incubators. Using it, researchers can reduce their reliance on core facilities, which can often be busy and expensive. The images taken with the CytoSMART Device are automatically transmitted into the cloud, enabling researchers to view their cell culture outside of the laboratory at any time through a web browser, whether via a computer, tablet or smartphone.

Advanced functions of the CytoSMART System include reporting ongoing cell confluency via a graphical readout and generating automatic email alerts to inform the user when milestones are reached. In addition to confluence studies, the CytoSMART System is well suited for scratch assays and for cells grown under hypoxic conditions as they don't need to be removed from the incubator for assessment.

The first laboratory to use the CytoSMART System in this brand-new initiative is the Department of Anatomy and Cell Biology, part of the Medical Faculty at the Martin Luther University Halle-Wittenberg. Researcher Trutz-Eckhardt Fischer concludes, "The CytoSMART System completely fulfills our needs and is an adequate option for all cell-tracking tasks where a high resolution or fluorescence is not required. The big advantage in comparison to "traditional" live cell imaging systems certainly is the small size and the possibility to use the device in your already existing incubator, with no need for further investments."

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Not only are we a custom manufacturer and developer, Lonza also offers services and products ranging from active pharmaceutical ingredients and stem-cell therapies to drinking water sanitizers, from the vitamin B3 compounds and organic personal care ingredients to agricultural products, and from industrial preservatives to microbial control solutions that combat dangerous viruses, bacteria and other pathogens.

Immune Design & Gritstone Oncology Announce Clinical Collaboration

Immune Design and Gritstone Oncology recently announced a clinical collaboration for development of novel, personalized immunotherapies combining both companies' leading technologies.

The collaboration will involve the application of Immune Design's ZVex discovery platform with Gritstone's proprietary genomics and proteomics platform for identification of patient-specific tumor antigens to develop neoantigen-based immunotherapies. Immune Design and Gritstone will be jointly responsible for development activities, with an initial likely focus in non-small cell lung cancer. The first clinical trial is expected to commence in 2017.

"The emerging tumor neoantigen field holds great potential for the successful application of cancer immunotherapies, and we are pleased to be working with Gritstone, a company that we believe is a pioneer in the field," said Carlos Paya, MD, PhD, President and Chief Executive Officer of Immune Design. "Having validated our two platforms in clinical trials targeting conserved tumor antigens, we believe their application to patient specific tumor antigens is a natural next step."

For the first trial of their technologies, the companies are evaluating combining the Gritstone and Immune Design neoantigen vaccine with a checkpoint inhibitor, to optimize the vaccine-induced immune response at several levels and maximize the likelihood of clinical efficacy.

"We are excited to work with Immune Design and their novel immunotherapy approach," said Andrew Allen, MD, PhD, Co-founder, President and Chief Executive Officer of Gritstone Oncology. "There is good evidence that viral vectors are one of the most effective means of generating high titer CD8+ T cells that recognize encoded antigens, and so this is a logical move for our company, as our neoantigen prediction platform starts to deliver immune targets for individual patients with lung cancer."

Immune Design is a clinical-stage immunotherapy company employing next-generation in vivo approaches to enable the body's immune system to fight chronic diseases. The company's technologies are engineered to activate the immune system's natural ability to generate and/or expand antigen-specific cytotoxic T cells, while also enhancing other immune effectors, to fight cancer and other chronic diseases. CMB305 and G100, the primary focus of Immune Design's ongoing immuno-oncology clinical programs, are products of its two synergistic discovery platforms, ZVex and GLAAS, the fundamental technologies of which were licensed from the California Institute of Technology and the Infectious Disease Research Institute (IDRI), respectively. Immune Design has offices in Seattle and South San Francisco.

Gritstone Oncology is a privately held cancer immunotherapy company developing next-generation personalized cancer therapeutics. Gritstone brings together distinguished scientific founders, an experienced and diverse management team, a seasoned and successful board of directors, and deep financial backing to tackle fundamental challenges at the intersection of cancer genomics, immunology, and immunotherapy design. The company's initial goal is to identify and deploy therapeutic neo-antigens from individual patients' tumor to develop novel treatments for lung cancer.

REGENXBIO & Biogen Enter Exclusive License Agreement

REGENXBIO Inc. recently announced an exclusive worldwide license agreement with Biogen for the development of gene therapy product candidates based on the NAV Technology Platform for the treatment of two rare genetic vision disorders. The NAV Technology Platform is an AAV gene delivery platform consisting of exclusive rights to more than 100 novel AAV vectors, including AAV7, AAV8, AAV9, and AAVrh10.

Under the terms of the agreement, REGENXBIO has granted Biogen an exclusive worldwide research license, with rights to sublicense, to REGENXBIO's NAV AAV8 and AAV9 vectors for the development of gene therapy product candidates for the treatment of two rare genetic vision disorders in humans. Upon selection of a single vector for each indication, the research license will convert to a commercial license. In return for these rights, REGENXBIO will receive an undisclosed upfront payment, ongoing fees, milestone payments, and royalties on net sales of products incorporating the licensed intellectual property.

"This license agreement provides new validation of the potential of our NAV Technology Platform in ocular indications and is an important step in advancing NAV-based gene therapies to people suffering from rare genetic vision disorders," said Kenneth T. Mills, President and CEO of REGENXBIO. "We are pleased that Biogen, a respected biotechnology leader, has selected our NAV Technology Platform for the development of innovative gene therapies to improve treatment options in areas of significant unmet need."

"We're continually looking for opportunities to advance gene therapies to people lacking adequate treatments, through improved delivery vectors, like REGENXBIO's NAV Technology Platform," added Olivier Danos, PhD, Senior Vice President, Cell & Gene Therapy at Biogen. "This collaboration will enable us to expand our pipeline of treatments with the potential to improve health outcomes in diseases of the eye, an ideal setting for the delivery of targeted gene therapies."

Through cutting-edge science and medicine, Biogen discovers, develops, and delivers worldwide innovative therapies for people living with serious neurological, autoimmune, and rare diseases. Founded in 1978, Biogen is one of the world's oldest independent biotechnology companies and patients worldwide benefit from its leading multiple sclerosis and innovative hemophilia therapies. For more information, visit www.biogen.com.

REGENXBIO is a leading biotechnology company focused on the development, commercialization, and licensing of recombinant adeno-associated virus (AAV) gene therapy. REGENXBIO's NAV Technology Platform, a proprietary AAV gene delivery platform, consists of exclusive rights to more than 100 novel AAV vectors, including AAV7, AAV8, AAV9, and AAVrh10. REGENXBIO's mission is to transform the lives of patients suffering from severe diseases with significant unmet medical need by developing and commercializing in vivo gene therapy products based on REGENXBIO's NAV Technology Platform. REGENXBIO seeks to accomplish this mission through a combination of internal development efforts and third-party NAV Technology Platform licensees.

Incyte & Ariad Announce Acquisition & Licensing Agreements

Incyte Corporation and ARIAD Pharmaceuticals, Inc. recently announced the entry into a definitive agreement for Incyte to acquire ARIAD's European operations. At the close of the transaction, the companies will also enter into a license agreement whereby Incyte will obtain an exclusive license to develop and commercialize Iclusig (ponatinib) in Europe and other select countries.

The planned acquisition of a fully integrated and established pan-European team of 125 employees, including medical, sales, and marketing personnel, will further Incyte's strategic plan and accelerate the establishment of its operations in Europe, helping to optimize clinical development and maximize the potential of future European launches for Incyte's portfolio of products in development.

The agreement to divest its European operations and out-license Iclusig in Europe will enable ARIAD to focus its promotion of Iclusig on the highly valuable US market, while strengthening its financial position and maintaining important optionality through a potential buy-back provision for the Iclusig license rights in the event of a change-in-control of ARIAD, as described further below.

Under the terms of the license agreement, Incyte will receive an exclusive license to develop and commercialize Iclusig, the only approved BCR-ABL inhibitor with activity against the T315I mutation, throughout Europe and in other select countries. Iclusig is approved in Europe for the treatment of patients with chronic myeloid leukemia (CML) and Philadelphia-positive (Ph+) acute lymphoblastic leukemia (ALL) who are resistant to or intolerant of certain second generation BCR-ABL inhibitors and all patients who have the T315I mutation.

Pursuant to the terms of a share purchase agreement (SPA), Incyte will acquire all shares of ARIAD Pharmaceuticals (Luxembourg) S.a.r.l., the parent company of ARIAD's European subsidiaries responsible for the commercialization of Iclusig in the licensed territory, for a payment to ARIAD of $140 million that will be funded by Incyte through available cash on hand.

In addition to the SPA, the parties have agreed to enter into a license agreement upon the closing of the SPA, pursuant to which Incyte will be granted an exclusive license to develop and commercialize Iclusig in the European Union and 22 other countries, including Switzerland, Norway, Turkey, Israel, and Russia. ARIAD will be entitled to receive tiered royalties of between 32% and 50% on net sales of Iclusig in the territory and up to $135 million in potential development and regulatory milestones for Iclusig in new oncology indications in the territory. ARIAD may also become eligible to receive additional milestones for non-oncology indications, if approved, in the territory. Incyte has also agreed to fund a portion of the ongoing clinical development of Iclusig in ARIAD's OPTIC and OPTIC-2L clinical trials through cost-sharing payments of up to $7 million in each of 2016 and 2017.

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LDC & Boehringer Ingelheim Join Forces to Discover Novel Approach for Schizophrenia Treatment

The Lead Discovery Center GmbH (LDC), Max Planck Innovation GmbH and Boehringer Ingelheim International GmbH have signed an agreement providing Boehringer Ingelheim with the option to receive the exclusive rights to a new lead compound for the treatment of schizophrenia to be discovered and developed at the LDC.

The novel approach builds on ground-breaking research results from Prof. Moritz Rossner and his team at the Max Planck Institute of Experimental Medicine in Göttingen. He will work closely together with the LDC team to identify and optimize novel compounds with strong therapeutic potential and develop it further to the stage of a validated pharmaceutical lead with in vivo efficacy. Moritz Rossner holds also a Professorship at Ludwig Maximilians University, Munich and is a co-founder of Systasy Bioscience GmbH.

Schizophrenia is a chronic, severe and disabling mental disorder ranked among the 12 most debilitating diseases by the World Health Organization. It affects about 1 in 100 people worldwide, changing the way they behave, think and perceive the world. Although anti-psychotic medications and psychosocial interventions can effectively reduce symptoms and improve patients' lives, there remains a strong need for new drugs truly addressing causative mechanisms and cognitive impairment.

In this early discovery project, Boehringer Ingelheim will take a seat on the project development team and will pay an option fee. In addition, the company will allocate internal resources to the program and support collaborating partners to strengthen the early development work. Once the project has attained proof-of-concept in relevant in vivo models Boehringer Ingelheim can exclusively license the lead at pre-defined terms for subsequent preclinical and clinical development. Any revenue the LDC may receive from commercialization will be shared with the academic inventors and collaborating institutions.

The Lead Discovery Center (LDC) was established in 2008 by the technology transfer organization Max Planck Innovation, as a novel approach to capitalize on the potential of excellent basic research for the discovery of new therapies for diseases with high medical need. The LDC takes on promising early stage projects from academia and transforms them into innovative pharmaceutical leads that reach initial proof-of-concept in animals. In close collaboration with high-profile partners from academia and industry, the LDC is building a strong and growing portfolio of small molecule programs with exceptional medical and commercial potential.

The LDC sustains a preferred partnership with the Max Planck Society and has formed alliances with AstraZeneca, Bayer, Merck Serono, Daiichi Sankyo, Qurient, Johnson & Johnson Innovation, Infinity Pharmaceuticals, and Roche as well as leading translational drug discovery centers around the globe.

Max Planck Innovation is responsible for the technology transfer of the Max Planck Society and, as such, serves as a link between industry and basic research. With its interdisciplinary team, it advises and supports scientists in evaluating their inventions, filing patents, and founding companies.

Vetter is a Winner of AbbVie TRIUMPH AWARD

AbbVie, one of the world's leading biopharmaceutical companies has awarded Vetter, a leading contract manufacturing and development organization (CDMO), the TRIUMPH AWARD for 2015. The award was granted for meeting AbbVie's predetermined high-level demands of service. Vetter received this prestigious award as a contract manufacturer in the category Third-Party Manufacturers - Supplier of the Year. Recently, Vetter announced that the company won two other coveted awards, the WorldStar Award 2016 for its syringe closure system Vetter-Ject, and the 2016 CMO Leadership Award in four categories including, quality, capabilities, expertise, and compatibility.

The AbbVie TRIUMPH AWARD was created to acknowledge contract service companies whose efforts are well-aligned with the company's business strategy, and make an important contribution to AbbVie's strategic vision on a long-term basis. With this award, granted within a field of more than 1,000 contractors, the company recognizes its top performing contract suppliers for efforts that consistently add measureable value, and regularly exceed best-in-class performance on behalf of AbbVie and patients who come to rely on their products. Vetter received this prestigious award as a contract manufacturer for 2015 in the category Third-Party Manufacturers - Supplier of the Year. This recognition was achieved by meeting the predetermined high-level demands of service AbbVie has come to expect that is 'consistently above-average.

"The winning of this award is especially significant for Vetter as it recognizes our continuing efforts to provide our customers a high level of service, and it is particularly gratifying since it is from one of the world's leading biopharmaceutical companies," said Vetter Managing Director Peter Soelkner. "This award is a reflection of the value that Vetter brings to the biopharmaceutical industry, and consequently to patients worldwide, and is yet another affirmation that Vetter continues to exceed the expectations of our peers in areas of critical importance to their business."

Vetter is a global leader in the fill and finish of aseptically prefilled syringe systems, cartridges and vials. Headquartered in Ravensburg, Germany, with production facilities in Germany and the United States, the contract development and manufacturing organization (CDMO) is an innovative solution provider serving the top 10 (bio-)pharmaceutical companies, as well as small and midsize companies. Its portfolio spans state-of-the-art manufacturing from early clinical development through commercial filling and final packaging of parenteral drugs. The company's extensive experience covers a broad range of complex compounds including monoclonal antibodies, peptides and interferons. Vetter supports its customers every step of the way, guiding their products through development, regulatory approval, launch and lifecycle management. Known for quality, the company of approximately 3,600 employees offers a foundation of experience spanning more than 35 years, including dozens of customer product approvals for novel (bio-)pharmaceutical compounds.

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MICROBIAL PRODUCTION

Cutting-Edge inABLE® Technology: The Key to Cost-Effective Production of a Novel Antimicrobial Peptide With Potential for the Treatment of MRSA

By: Ian Fotheringham, PhD, and Mathew Upton, PhD

ABSTRACT

Infections caused by antibiotic resistant bacteria are an ever-increasing threat to public health, creating an urgent, growing demand for the identification and development of new therapies. One class of compounds showing promise is the bacteriocins – short peptides produced by bacteria – which have demonstrated good activity against a number of human pathogens. The bacteriocins group includes epidermicin, a recently discovered novel antimicrobial peptide that has shown great potential during initial studies. However, epidermicin is produced in very low amounts in its native host, and synthetic production is prohibitively expensive. Biotechnology company Ingenza and scientists at Plymouth University School of Biomedical and Healthcare Sciences, supported by an award from the InnovateUK Industrial Biotechnology Catalyst scheme, are engaged in a collaborative project using proprietary inABLE® technology to develop an efficient, scalable microbial production system. This will enable larger amounts of epidermicin to be cost-effectively produced for further investigation.

INTRODUCTION

Antibiotic resistance is an escalating problem, making the development of effective new therapies crucial. Bacteriocins – ribosomally synthesized antimicrobial peptides – have the potential to meet this need. Compared to the broad spectrum of classical antimicrobial agents, bacteriocins display a relatively narrow range of inhibition. This may be an advantage, as narrow spectrum agents, which target specific bacteria, are thought less likely to lead to the development of antibacterial resistance. Epidermicin, a peptide produced by some staphylococci, is a member of the bacteriocin class of compounds. This exciting new antibiotic rapidly kills methicillin-resistant *Staphylococcus aureus* (MRSA) and other bacteria, and offers significant advantages compared to existing antibiotics as it is more potent and non-toxic, and bacteria do not appear to easily develop resistance to it.

INVESTIGATING EPIDERMICIN

Epidermicin was originally discovered in a strain of *Staphylococcus epidermidis* during an independent research project into antimicrobial peptides performed at the University of Manchester.[1] Characterization showed it to be a very potent, stable, 51 amino acid peptide that was effective against Gram-positive bacteria, such as staphylococci, streptococci, and enterococci.

Epidermicin exerts its effect by perforating the bacterial cell membrane. In standard laboratory assays, it does not kill *Escherichia coli*, a Gram-negative bacterium; however, if you try to make *E. coli* produce epidermicin internally, the membrane is attacked from within the cell, and the bacterium is

"The development of any potential pharmaceutical preparation is only viable if it can be produced in a cost-effective manner on a large scale. A partnership with an industrial biotechnology company seemed the way forward, and this led to a collaboration between researchers at Plymouth University School of Biomedical and Healthcare Sciences and Edinburgh-based biotechnology company Ingenza, taking advantage of the company's cutting-edge inABLE technology to develop an efficient, scalable microbial production system."

destroyed. Often, bacteriocins are modified within bacteria, increasing their stability, affecting their mode of action and consequently making them more complicated to synthesize. In contrast, epidermicin is an unmodified peptide and, in theory, therefore more straightforward to make.

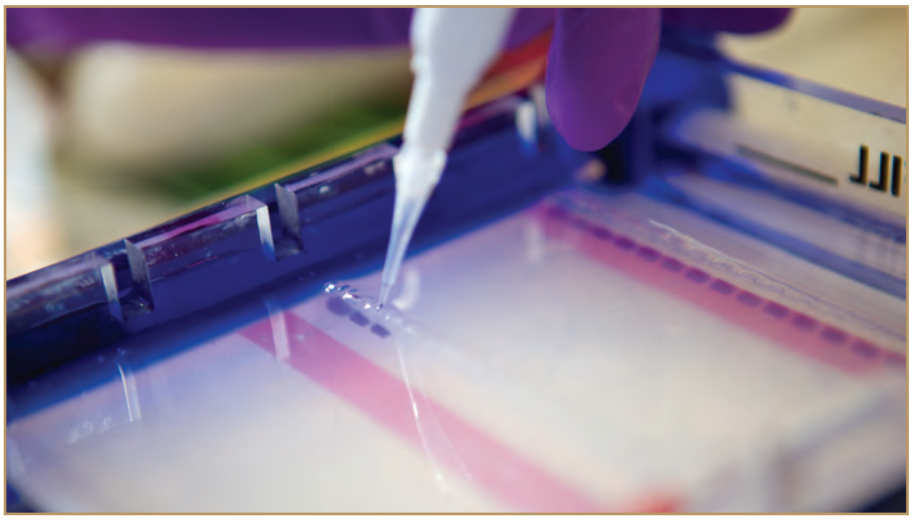
Industry, academic, and clinical experts were of the opinion that the best application for epidermicin would be nasal decolonization of MRSA, and this was investigated using cotton rats as a representative model. The rats were decolonized nasally for *S. aureus*, left for a couple of days, and then colonized with MRSA. Once colonization was established, the rats were divided into three groups; a) used as controls, b) treated with a vehicle or given a single dose of epidermicin, or c) administered epidermicin or mupirocin twice daily for 3 days. The results showed that a single high dose of epidermicin was as effective as six doses of mupirocin. With the initial *in vivo* data from an animal trial demonstrating the efficacy of epidermicin against MRSA, complemented by very good *in vitro* data, researchers could now justify taking the compound forward for further studies. However, epidermicin is only produced in very low amounts in its native host and synthetic chemical production of such peptides is prohibitively expensive; despite being unmodified, epidermicin is still not easy to produce using standard fermentation approaches. This was a big stumbling block for the use of this compound in clinical environments.

A SYNTHETIC CHALLENGE

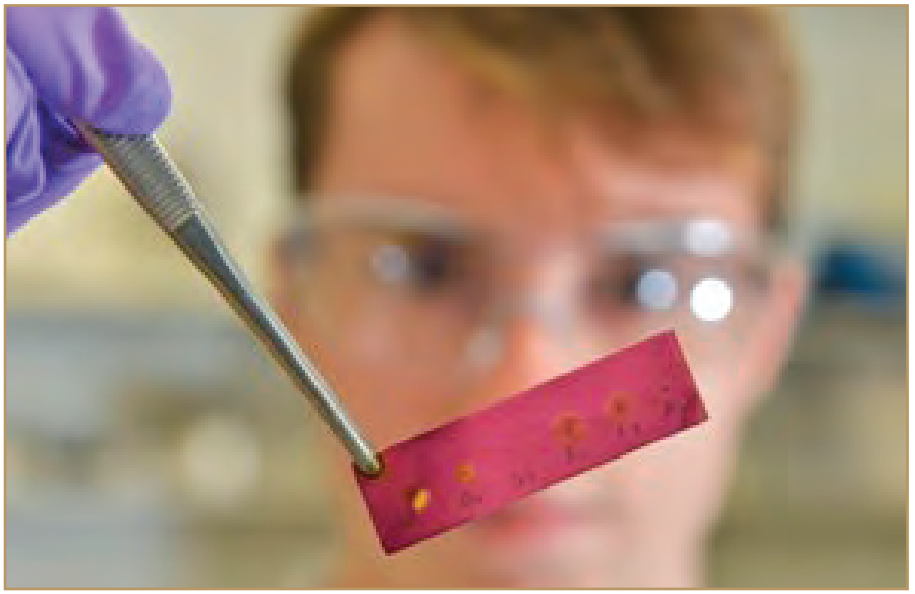
The development of any potential pharmaceutical preparation is only viable if it can be produced in a cost-effective manner on a large scale. A partnership with an industrial biotechnology company seemed the way forward, and this led to a collaboration between researchers at Plymouth University School of Biomedical and Healthcare Sciences and Edinburgh-based biotechnology company Ingenza, taking advantage of the company's cutting-edge inABLE technology to develop an efficient, scalable microbial production system.

A NOVEL APPROACH TO PRODUCTION

Ingenza, a world leader in the application of industrial biotechnology and synthetic biology, is engaged in the development of bio-based manufacturing routes that are environmentally sustainable in the long term. The



company has two potential approaches to developing production systems; using an alternative microbial host, such as yeast, or its inABLE technology. Yeast is frequently used as a production microbe in fields ranging from pharmaceuticals to biofuels, and the company's robust, reliable, scalable fermentation capabilities made it a possible option for further investigation. It is not affected by bacteriocins, and would be expected to allow efficient production of the peptide as well as secretion into culture medium – which is a big advantage as it makes purification of the molecule easier – and can be scaled up to large volumes. The alternative route took advantage of Ingenza's inABLE technology – a proprietary set of tools that enhances many critical aspects of recombinant protein synthesis, enzyme evolution, and biochemical pathway engineering for commercial applications – to deliver an innovative combinatorial approach. This approach significantly increases the efficiency with which large numbers of diverse genetic constructs can be combined, rearranged, and evaluated *in vivo*, helping to accelerate the successful commercialization of new biological entities and bioprocesses.



A SYMBIOTIC RELATIONSHIP

The technologies used by Ingenza to express difficult peptides and proteins were an ideal match for Plymouth's research studies, and both groups were keen to develop a long-term relationship. After successfully applying for an IB Catalyst (Innovate UK/BBSRC) grant, the teams embarked on a collaborative project to develop an integrated synthetic biology approach for efficient production of epidermicin.

The researchers had two objectives; increasing the breadth of the antimicrobial peptide portfolio and enabling the cost-effective production of large amounts of epidermicin. Ongoing postdoctoral research at Plymouth has centered on expanding the range of similar antimicrobial peptides, using an informatics approach to try to find new entities with different activities. Scientists have already established that it is possible to modify these proteins, engineering their genetic structure – for example by truncation – to introduce novel activity. By changing the specificity, the protein's activity could then be targeted toward other pathogenic bacteria. Although the initial focus was primarily on MRSA, epidermicin has now been shown to have potential for topical application for predominantly Gram-positive indications, such as impetigo, and also demonstrates very good activity against vancomycin-resistant enterococci (VRE). However, Gram-negative pathogens are actually considered more of a problem and, by modifying the structure of epidermicin, it may be possible to develop a peptide with activity against these bacteria. This would enhance the commercial viability of the

product, as the market size for any single organism is quite small; with a broader range of activity against a variety of bacteria, its value increases considerably.

Plymouth's rational design and informatics approach is complemented by Ingenza's combinatorial methodology, a semi-randomized, high throughput production and selection process using inABLE technology. To obtain maximum benefit, epidermicin needs to be modified in many different ways and then screened to determine which of the genetic changes are the most effective. Here, scientists can learn from nature, copying successful processes in the laboratory, effectively mimicking biology to make random genetic mutations for screening and selection. Antibiotics are an ideal group of compounds to investigate in this manner. Bacteria can be colored to make visualization easier and applied to microplates to monitor the inhibitory effect of the antibiotic, enabling the most effective modifications to be identified.

Using inABLE technology, thousands of different changes can be engineered into the DNA sequence of epidermicin, changing the structure of the protein. Entire families of proteins can also be investigated, combining the production of multiple proteins in one system. This allows many more modified versions of epidermicin to be produced which, along with natural or modified versions of the family of proteins in which it exists in nature, are then tested against a range of pathogens. A single modified version of epidermicin or a combination of proteins with a greater breadth of applicability can be identified more rapidly, enabling a broader host range active against many different bacterial hosts – or with higher efficacy – to be developed in a shorter time frame, accelerating evolution.

A COMMERCIALLY VIABLE PROPOSITION

Increasing the breadth of the antimicrobial peptide portfolio is just one part of the collaborative study. The other key aspect of the project is the cost-effective production of epidermicin, and Ingenza's state-of-the-art technology is being used to develop an efficient, scalable microbial production system that can generate commercially viable amounts of the compound, as well as offering the flexibility to produce other antimicrobial peptides in the future. The ultimate goal is to establish a method that produces from tens to hundreds of milligrams of peptide per liter of culture grown. Based on the costing model prepared, yields of this magnitude should make the production of epidermicin a commercially viable prospect. By the time the current 2-year IB Catalyst (Innovate UK/BBSRC) grant funded project reaches completion, the aim is to be producing sufficient peptide to carry out preclinical toxicity formulation and stability studies. In time, this should then lead to the initiation of a Phase I clinical trial. The hope is that work that could conceivably have taken 10 years using conventional practices will be completed within the 2-year time frame, drawing the project to a perfect conclusion. ◆

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BIOGRAPHIES

Dr. Ian Fotheringham earned his PhD in Molecular Biology from the University of Glasgow, UK, in 1986. He joined the NutraSweet division of Monsanto in Chicago, IL, constructing microbes to produce the Aspartame® sweetener. From 1993, he continued developing large-scale bioprocesses with NSC Technologies and Great Lakes Fine Chemicals. In 2003, he co-founded Ingenza, an Edinburgh, UK-based Industrial Biotechnology SME with a unique range of proprietary enabling technologies. Now a leader in microbial strain improvement, synthetic biology, fermentation, and bioprocess development, Ingenza works with industrial partners worldwide to commercialize state-of-the-art biomanufacturing processes. Dr. Fotheringham has published 35 papers and articles and holds 8 current patents.

Dr. Mathew Upton is a Reader in Medical Microbiology at Plymouth University and Co-founder and Director at Spectromics Ltd, a University of Manchester spin-out that formed in April 2014. He earned his PhD in Microbial Ecology at the University of Newcastle upon Tyne. His expertise in medical microbiology developed during several postdoctoral projects, the last of which was with Prof. John Tagg in New Zealand, where he studied the genetics of antimicrobial peptide production in Streptococci. Dr. Upton took a Lectureship in Medical Microbiology at the University of Manchester in 2001, was promoted to Senior Lecturer in 2011, and moved to Plymouth in May 2013. He has authored over 60 peer-reviewed papers and holds 5 patents. Members of his group investigate bacterial pathogenesis and run a program of natural product screening for discovery of novel bacteriocins, antimicrobial peptides produced by bacteria. The lead compound, epidermicin, is being developed toward clinical use for prevention and therapy of skin infections, with commercially focused funding from a range of Research Council and other sources.

LIPOPHILIC SALTS

Opportunities & Applications in Oral Drug Delivery

By: Hywel Williams, PhD, Annabel Igonin, PhD, David Vodak, PhD, and Hassan Benameur, PhD

INTRODUCTION

A salt form of an active pharmaceutical ingredient (API) will exhibit distinctive solid-state and solution properties relative to the free acid or free base form. For this reason, pharmaceutical salts are commonly explored to address formulation and/or biopharmaceutical-related issues, such as poor aqueous solubility, slow dissolution rate, poor chemical stability, unacceptable taste, or physical stability issues, such as crystalline polymorphism.[1]

Traditional salt-forming screening strategies to promote aqueous API solubility, for example, have employed inorganic or small organic counterions. In oral drug delivery, the most commonly used counterions over the past three decades include hydrochloride, maleate, mesylate, and phosphate for basic drugs, and calcium, magnesium, potassium, and sodium for acidic drugs.[2] More recently, there has been a growing interest in lipophilic salt forms that exhibit lower melting points than respective free acid/base forms, particularly those that have a melting point or glass transition below 100°C.[3] Such materials may be referred to as "Ionic Liquids," which were first described by Paul Walden in 1914 who reported that the salt, ethylammonium nitrate with a melting point (T_m) of 12°C, was physically stable in the liquid state at room temperature.

As described in this short review, it is possible to prepare lipophilic salts and even Ionic Liquid forms of a range of APIs for the purpose of formulating these in concentrated lipid formulations ready for oral delivery. Preliminary *in vitro* and *in vivo* studies also indicate that this salt selection approach is enabling to lipid formulations by supporting substantially higher loadings (>10-fold in some cases) than otherwise possible using free API. The use of lipophilic salts therefore grants a greater number of API access to the well-established benefits of lipid formulations by, for example, overcoming certain product design constraints, such as the number and/or size of dosage unit.

APPLICATIONS OF LIPOPHILIC SALTS/IONIC LIQUIDS IN DRUG DELIVERY

Ionic liquids are a well-established class of materials with present day applications in different areas, including biomass processing, renewable energy, synthesis, and analytical chemistry.[4] In drug delivery, ionic liquids have been explored as "designer solvents" whereby ionic liquid structure (and therefore solvent capacity) is fine-tuned through structural changes to the cation or anion, or by simply exploring different anion-cation combinations.[5,6] In terms of their application, designer ionic liquid solvents may be used for cleaner reactions if employed during drug synthesis and extraction,[7] while ionic liquids as cosolvents can also enable higher API loadings in liquid formulations.[5]

It is also possible to isolate salt forms of an API that exhibit depressed melting points relative to the free acid or base, and those salts that meet the ionic liquid definition (T_m/T_g < 100°C) have been described as active API-ionic liquids (API-ILs). Here, we use the term "lipophilic salts" to describe salts (including

API-ILs) that exhibit higher solubilities in commonly used lipid vehicles in comparison to the free acid or base API form.

Due to their distinct physical and solution properties relative to their higher melting counterparts, lipophilic salts are being explored for:

- circumventing crystal polymorphism issues[8]
- increasing aqueous solubility for oral[9,10] or parenteral drug delivery[10]
- dual function salts combining anion and cation actives in one complex for combined, unique or enhanced pharmacological/pharmacodynamics or biopharmaceutical effects[11,12]
- enhanced permeation across hydrophobic barriers, eg, the skin[12]
- enhanced API loading in lipid-based formulations[13]

Across these explored applications, Table 1 lists some example lipophilic salt forms that have been described in the literature, alongside respective melting points (T_m) or glass transition (T_g) temperatures, and the reported advantage of the novel salt form.

This list exemplifies the potential of forming lipophilic salts and sometimes ionic liquids from a range of both weakly acidic and basic API. It also demonstrates that these unique salt forms may be formed from a number of different counterions that have past or current applications in drug delivery.

TABLE 1

Lipophilic Salt of Basic API	Thermal Property	Reported Advantage	Reference
Lidocaine salicylate	~ - 30ºC (T_g)	Dual function salt – antiarrhythmic and anti-inflammatory properties	14,15
Metformin docusate	~ - 27ºC (T_g)	none described	
Bupivacaine acesulfame	~ 19ºC (T_g)	Dual function salt, with improved taste for oral drug delivery	14
Cinnarizine decylsulfate	~ 7ºC (T_g)	↑ API loading in lipid formulations for oral drug delivery	13,16
Itraconazole docusate	~ 26ºC (T_g)		
Itraconazole lauryl sulfate	~145ºC (T_m)		
Fexofenadine lauryl sulfate	~ 50ºC (T_g)		
Ranitidine docusate	~ - 12ºC (T_g)	↓ API crystal polymorphism	8,17
Propantheline acesulfamate	~ - 20ºC (T_g)		
Benzalkonium saccharinate	74ºC (T_m)	Dual function salt, with improved taste for oral drug delivery	18
Lipophilic Salt of Acidic API			
Etodolac lidocaine	< RT (T_m)	Improved transdermal API absorption	12
Ampicillin cholinium	58ºC (T_m)	None described	19
Tolbutamide tetrabutylphosphonium	56ºC (T_m)	↑ API aqueous solubility and dissolution for oral drug delivery	20
Diclofenac tetrabutylphosphonium	~120ºC (T_m)		
Sulfadiazine tetrabutylphosphonium	~110ºC (T_m)		
Ibuprofen tetrabutylphosphonium	< 0ºC (T_g)		
Ketoprofen tetrabutylphosphonium	<0 ºC (T_g)		
Sulfasalazine cholinium	~ 59ºC(T_g)	↑ API aqueous solubility for parenteral drug delivery	10

Select lipophilic salts described in the literature, respective T_m or T_g values and reported advantage. Those with a T_m/T_g < 100°C can also be classed as ionic liquids.

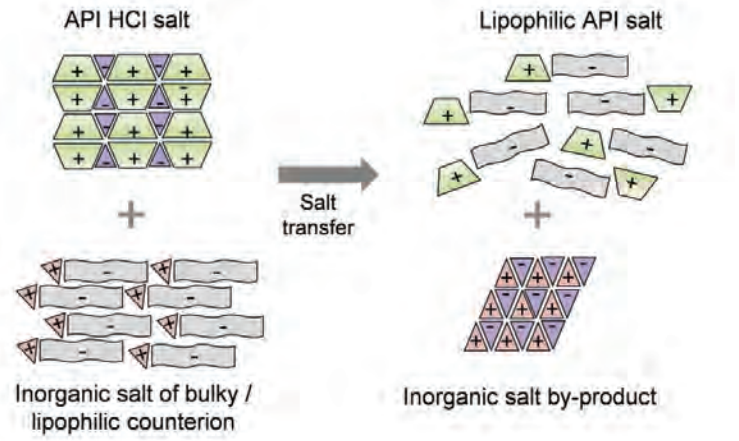
LIPOPHILIC SALT FORM DESIGN, PREPARATION & CHARACTERIZATION

The formation of a tightly packed crystalline structure in conventional, high-melting point salts is driven by the reduction in entropy and formation of strong electrostatic interactions between oppositely charged ions that result in high enthalpy. In contrast, due to a more disordered state, lipophilic salts have higher entropy. Stability in this more disordered state can, however, be achieved if electrostatic forces between anions and cations are sufficiently weak to offset the higher entropy. Common features of anions and/or cations designed to minimize the strength of electrostatic forces and depress melting therefore include (1) larger ions to increase distance between intercharge distance and to introduce asymmetry, and (2) lower charge density (due to charge delocalization) to decrease charge magnitude.[4] Along with electrostatic forces, the hydrogen bonding potential between ions can be intentionally minimized to further reduce melting temperatures, for example, by using hydrophobic ions such as alkyl sulfates or alkyl amines.

Different techniques have been employed to synthesize lipophilic salts, though a great many have been prepared by salt metathesis reactions, for example, using a hydrochloride salt of a weakly basic API and a sodium salt of a bulky/lipophilic anionic counterion (Figure 1). Driven by the formation of an inorganic salt by-product and the differential solvent solubility of the reaction products, a salt interchange proceeds, yielding the low-melting salt of basic API and acidic counterion dissolved in the solvent phase.

Following removal of the solvent, salt formation may be confirmed through ^{1}H NMR and/or infrared spectroscopy. Thermal tests, for example DSC, are then performed to determine the salt melting point/glass transition temperature, particularly to determine if it qualifies as an ionic liquid.

FIGURE 1



Schematic depicting change in ionic packing following preparation of a lipophilic salt via a salt methathesis reaction.

Additional tests include; microscopy and/or XRD to define the physical form of the salt, NMR and/or TGA combined with gas chromatography to probe for residual solvent that may have carried over from the metathesis reaction into the recovered salt. Indeed, confidence that solvent level is low/negligible is particularly important since the presence of solvent may result in depressed melting point. If significant solvent levels are detected, refinement of the synthetic process or longer drying times may be needed. Recrystallization studies to explore the propensity for different salt physical forms may also be performed.

DEVELOPING LIPOPHILIC SALTS USING LIPID-BASED FORMULATIONS

While there is interest in using lipophilic salts in oral delivery, far less focus has been placed on identifying suitable delivery approaches for these API forms. Indeed, the low-melting and sometimes liquid-like nature of these salts (Table 1) make incorporation into standard dosage forms, such as tablets or powder-filled capsules, particularly challenging. On the other hand, lipid-based formulations have precedence in the delivery of low melting, lipophilic actives [as liquid or semi-solid filled capsules], for example, dronabinol (Marinol®), fish oils, polyunsaturated fatty acids, and crude biological extracts.

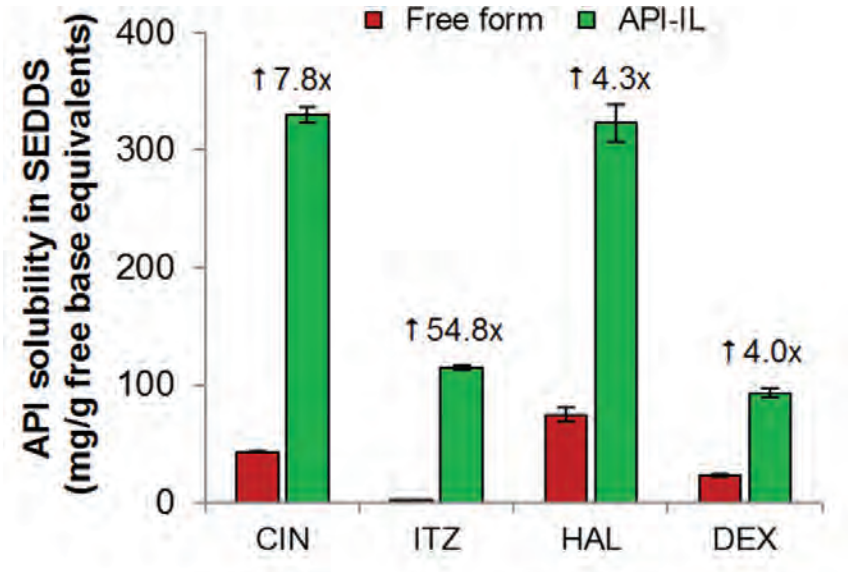
The potential to use lipid-based formulations to formulate lipophilic salts, including API-ILs, was first shown by researchers at Monash University in Melbourne, Australia, in a pivotal *in vitro* and *in vivo* study.[13] This study not only showed that API-ILs could be effectively absorbed from lipid formulations, it revealed their strong synergy with lipids; API-ILs were substantially more lipid soluble in comparison to the free API and, thus, enabled much higher loadings in the lipid formulations. This enhanced lipid solubility of API-ILs is illustrated in Figure 2 for four weakly basic APIs, namely cinnarizine (T_m = 118°C), itraconazole (T_m = 170°C), halofantrine (T_m = 79°C-82°C) and dextromethorphan (T_m = 111°C). In each case, when combined with an acidic lipophilic counterion, an API-IL was formed that, in turn, exhibited markedly higher solubility in a self-emulsifying lipid formulation (SEDDS) in comparison to the free base form. For example, the solubility of cinnarizine free base in the SEDDS was only 43.2 mg/g, whereas the solubility of the API-IL cinnarizine decylsulfate (T_g = 7°C) was > 300 mg/g, when expressed as cinnarizine free base equivalents.

These dramatic increases in lipid solubility may be ascribed primarily to the absence of the crystalline lattice in the API-IL form (evidenced by a lack of a melting point) and the use of a lipid-soluble counterion. Complete elimination of crystallinity is not essential to substantial increases in lipid solubility. For example, despite only a decrease in melting point of ~20°C, the lipophilic salt, itraconazole lauryl sulfate (T_m = 145°C -150°C) was over ten times more lipid soluble than itraconazole free base.[13]

API solubility in lipid formulation is important to development since it guides the maximal possible loading in solution-type lipid formulations. Use of highly lipid-soluble salt forms therefore translated to increased API loadings. For cinnarizine, loading was limited to 35 mg/g using the free base, but was boosted to > 125 mg/g when using an API-IL form. Similarly, for itraconazole, the very low solubility of the free base precluded loadings > 1-2 mg/g while ~100 mg/g was feasible using the API-IL form. Crucially, for these two poorly water-soluble APIs, this increase in loading did not result in an increased risk of *in vitro* precipitation post dispersion and digestion.[13]

The use of API-ILs enabled *in vivo* dosing of highly concentrated SEDDS-type formulations, whereas in comparison, equal doses of free base

FIGURE 2



Graph depicting the lipid solubility and loading advantage of using API-IL forms of a compound. CIN: cinnarizine. ITZ: itraconazole. HAL: halofantrine. DEX: dextromethorphan. API-IL forms were decylsulfate, oleate or docusate salts. (Adapted from Sahbaz et al.[13])

APIs could only be dosed as suspension formulations. As illustrated in Figure 3, at a 125 mg/g loading, the API-IL containing SEDDS yielded 2-fold higher cinnarizine plasma exposure over the SEDDS containing free base API (lipid suspension), and 3.5-fold higher exposure compared to an API free base aqueous suspension. Figure 3 also highlights the increase in exposure on increasing cinnarizine loading in the SEDDS ~3.5 fold from 35 mg/g (the maximum loading for the free base API) to 125 mg/g when using the API-IL form and with no increase in formulation volume.

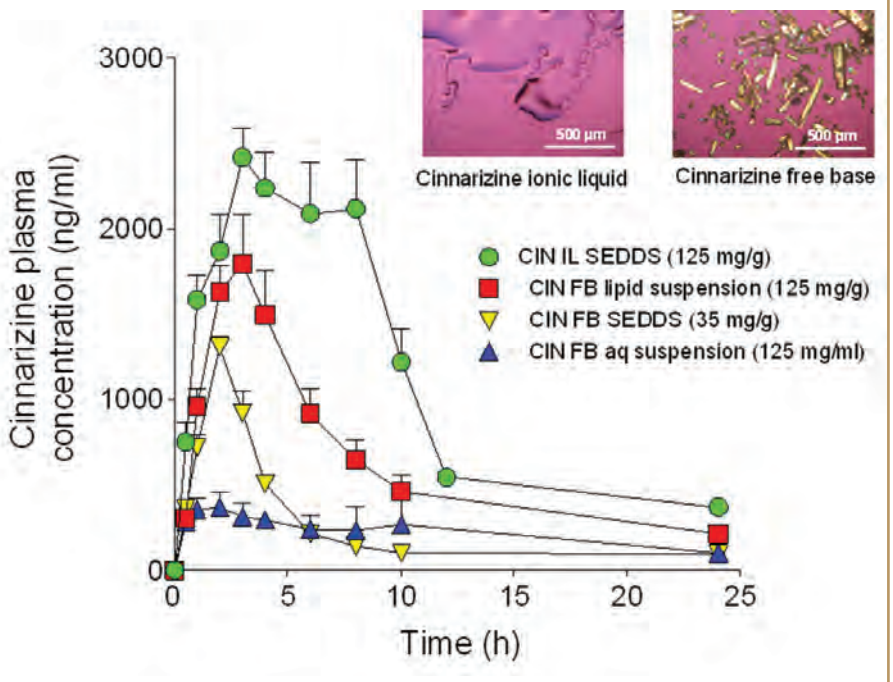
Equally encouraging results were reported for itraconazole, which is notoriously water and lipid insoluble. Indeed, the API-IL itraconazole docusate (T_g = 26°C) showed a > 50-fold increase in solubility in lipid formulations (Figure 2), and offered a 2-3-fold increase in exposure over the currently marketed amorphous drug formulation (Sporanox®).[13]

Transformation of API into more lipid-soluble salts is not only limited to poorly water-soluble compounds. For example, the solubility of dextromethorphan in the SEDDS increased from 23.5 mg/g to 93.3 mg when an API-IL form (dextromethorphan decylsulfate, T_m = 62°C-68°C) was used (Figure 2).

SUMMARY

We define lipophilic salts as salts having increased solubility in lipidic vehicles relative to free base or acid API form. Inclusive in this definition are API-ionic liquids (salts melting below 100°C) because melting point depression can promote solubility in non-aqueous vehicles. Lipophilic salts are being explored in a number of different areas,

FIGURE 3



The higher solubility of the API-IL cinnarizine decylsulfate in lipid formulations enabled a 3.5-fold increase in loading (and therefore dose) to be administered to rats as a lipid solution SEDDS, with no increase in formulation volume. The pharmacokinetic profiles highlight the utility API-ILs for lipid formulations. (Modified from Sahbaz et al.[13])

"Lipid formulations have proven applications in enhancing oral bioavailability and providing a rapid onset of action. Access to more lipid soluble forms of API broadens these applications of lipid formulations as increased lipid solubility allows higher API loadings and therefore the need for a fewer number or smaller size dosage forms. As this increase in solubility is achieved with no covalent change in the API structure, the use of lipophilic salts does not raise the same questions of receptor promiscuity and potential off-target toxicity that are commonly associated with intrinsically lipophilic molecules (since the lipophilicity of the API remains unchanged)."

and as overviewed in this article, one interesting application is their potential to boost API loading in lipid formulations. Lipid formulations have proven applications in enhancing oral bioavailability and providing a rapid onset of action. Access to more lipid soluble forms of API broadens these applications of lipid formulations as increased lipid solubility allows higher API loadings and therefore the need for a fewer number or smaller size dosage forms. As this increase in solubility is achieved with no covalent change in the API structure, the use of lipophilic salts does not raise the same questions of receptor promiscuity and potential off-target toxicity that are commonly associated with intrinsically lipophilic molecules (since the lipophilicity of the API remains unchanged). Lipophilic salts may be also be prepared using alkyl sulfates, docusate, and fatty acid-based anionic counterions, which have wide use in oral drug products, either as counterions, excipients or excipient components.

Capsugel Dosage Form Solutions continues to invest heavily in its bioavailability enhancement technology platform, which includes spray-dried dispersions, hot-melt extrusion, particle engineering/nanocrystal technology approaches, in addition to lipid-based solutions. We have established a Capsugel-Monash collaboration specifically with the objective of furthering our understanding of lipophilic salts and their applications. For example, we are currently exploring in greater depth the biopharmaceutical aspects of lipophilic salts and the impact of lipid formulations, while we are also confirming that our formulation development approach based on our proprietary lipid expert system[21] fits with lipophilic salt forms including API-ILs. With this knowledge, we will be able offer our customers rational design of lipophilic salt formulations to support for preclinical and clinical testing of poorly water-soluble drugs, where lipid-based formulations are determined as an optimal approach or to support new product opportunities for existing API. ◆

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BIOGRAPHIES

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Dr. David Vodak is Senior Director, Pharma R&D at Capsugel, where his responsibilities include overseeing the development of new pharmaceutical delivery platforms, including bioenhancement, particle engineering, and functional modified-release platforms. He earned his BA in Chemistry from Willamette University and his PhD in Materials Science from the University of Michigan-Ann Arbor.

Dr. Hassan Benameur is Senior Director, Pharmaceutical Sciences at Capsugel with over 20 years of expertise in advanced drug delivery development. Dr. Benameur's expertise is in novel polymer applications for drug delivery and optimized lipid-based formulations for enhanced absorption to maximize success and reduce attrition in pharmaceutical product development. He is a Chemical Engineer and earned his PhD in Pharmaceutical Sciences from the Free University of Brussels in Belgium.

Dr. Annabel Igonin is Senior Manager, R&D Pharmaceutical Drug Delivery and New Technologies, at Capsugel's Strasbourg, France, facility. She leads key R&D initiatives for novel lipid-based formulation technologies for bioavailability enhancement with challenging APIs and the development of Rx and OTC products. Dr. Igonin earned her Pharmacy degree from the University of Lyon, France.

CARBON NANOTUBES

MGMR™ - A Medical-Grade Carbon Nanotube Designed for Medical Applications

By: Joseph S. Dillon, PhD, MBA, and Lainie Mulvanny

INTRODUCTION

Since their discovery in 1991, carbon nanotubes (CNTs) were an exciting possibility for the medical research community to overcome barriers in a wide variety of applications including: drug delivery, regenerative medicine, gene therapy, bio-sensors, orthotics, devices, immunotherapy, diagnostics, and material optimization. Yet while CNT research has evolved over the past quarter century, some obstacles still needed to be overcome for widespread medical application. Achieving a scalable technology to make discrete, clean, non-toxic consistent batches of functional carbon nanotubes has been elusive. Previously, no meaningful commercial use for CNTs had been established in the medical field due to these issues.

BioPact, a medical nanotechnology development company based in Cambridge, Massachusetts, has transformed CNTs into a unique composition of matter. This reimagined nanotube is known as Medical Grade Molecular Rebar, or MGMR™, and it marks a complete departure from the dirty, tangled micron bundles of CNTs that frustrated medical researchers for years. Now, pharmaceutical, biotechnology, and other medical product development programs can utilize the benefits of CNT properties though MGMR; the potential of the carbon nanotube in a practical application. BioPact is developing and partnering MGMR for use in medical applications addressing substantial unmet patient needs.

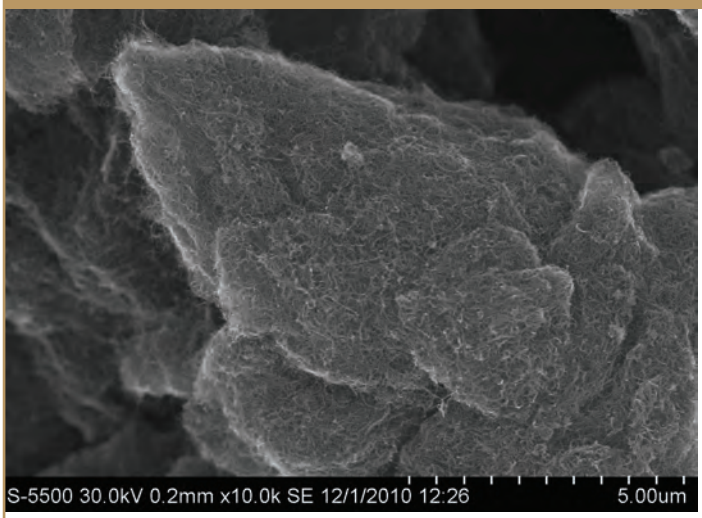
MGMR, A MAJOR BREAKTHROUGH

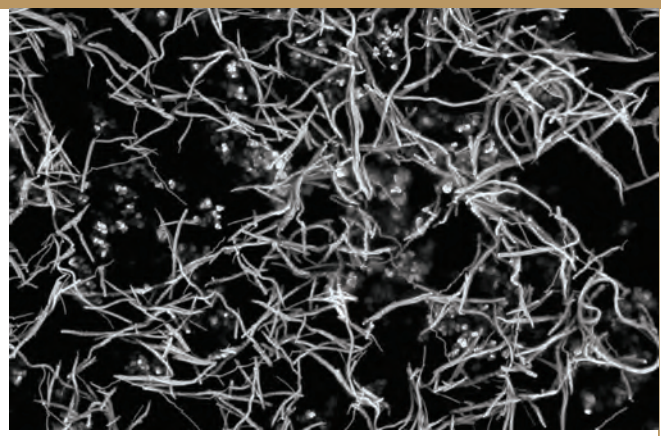
BioPact has developed a unique composition of matter and scalable process, protected by several granted and filed patents, to make the world's first medical-grade carbon nanotube. Medical Grade Molecular Rebar has demonstrated an unprecedented safety profile in studies commissioned by BioPact.

Less than a micron in length, MGMR is composed of individual, discrete, dispersed, length-controlled, surface-functionalized, multi-walled carbon nanotubes. Utilizing these advanced physical properties has allowed for the development of an exceptional drug delivery system when compared to liposomes, polymeric systems, and antibody drug conjugates.

MGMR carbon nanotubes hold tremendous potential in medicine due to their high aspect ratio: their relatively long length and small diameter means they have an extremely high surface area that allows them to enter cells and potentially cross the blood-brain barrier (BBB). The safety issues that are associated with working with traditional CNTs are no longer a concern with MGMR; no longer limiting the vast potential for advancement in an array of medical applications.

FIGURE 1





Traditional tangled micron bundles (left) vs. MGMR (right)

MGMR: SPECIFICATIONS & NOVEL PHYSICAL PROPERTIES

- Inner diameter = 4-5 nm
- Outer diameter = 12-14 nm
- Length = 900 nm
- Purity > 99.9%
- Discrete & dispersed
- Open ended tubes
- Surface functionalized
- Already manufactured at scale

IMPROVING MANUFACTURING PROCESS OF MGMR

Current manufacturing processes for CNTs leave behind traces of heavy and sometimes toxic metals, such as cadmium, lead, and alumina, which can leach out. This manufacturing process also frequently resulted in a "knotted amorphous mass" of tubes, ranging from a few microns to tens of microns long, that have lost their needle-like shape, and are associated with asbestos-like carcinogenicity problems seen in animal studies. MGMR can be produced economically, free of all metal impurities, and in discrete, ready-to-use form (Figure 1).

DRUG LOADING

Large or small molecules (e.g., proteins, peptides, antibodies) can be either covalently or non-covalently bonded to the exterior of MGMR (Figure 2).

Successful research performed to-date demonstrating loading and bonding of multiple substances to MGMR includes:

- Loaded insulin, chlorambucil, and bortezomib to the inside of MGMR.
- An enzyme and large molecule, horseradish peroxidase (HRP), was attached to the outer surface of MGMR both covalently and non-covalently. HRP remained strongly bound and retained function.
- Undecapeptide, QSYQAKANNYC, was attached to MGMR and labeled with tetramethyl rhodamine iodoacetamide. This peptide labeled MGMR was readily taken up by a variety of cell lines with no observed cytotoxicity. Many anti-angiogenic peptides are of similar length.
- Alendronate and Cy5 dye were covalently attached to the surface of MGMR using a standard bifunctional cross-linker. Fluorescence was observed, and bone targeting was successful. Both small molecules retained their function.
- Simultaneously loaded small dextran polymers and small molecule dyes into MGMR. The addition of the dextran polymer caused the release of the dye to occur over a longer period of time, demonstrating that both molecules were loaded into the interior of the MGMR and resulted in a method for controlled and sustained release.

BENEFITS OF MGMR

- Encapsulates API
- Protects API and is compatible with APIs regardless of hydrophobicity

"MGMR carbon nanotubes hold tremendous potential in medicine due to their high aspect ratio: their relatively long length and small diameter means they have an extremely high surface area that allows them to enter cells and potentially cross the blood-brain barrier (BBB). The safety issues that are associated with working with traditional CNTs are no longer a concern with MGMR; no longer limiting the vast potential for advancement in an array of medical applications. "

- Protects patients from potent drugs as they are targeted to the area of release
- Extremely high drug content to radius ratio
- Tunable release kinetics
- Penetrates cell readily and localizes to nucleus
- Expected to cross the blood brain barrier
- Excellent shelf stability
- Batch-to-batch consistency
- Potential to write new patents by applying MGMR to existing products

MGMR SAFETY

Animal studies have shown that MGMR is safe and free from side effects in multiple doses. Six doses of MGMR were injected over 18 days, all mice survived for the duration of study. No toxicity, no accumulation in organs, and extended circulation in blood was observed. The control group dosed with another "medical-grade" CNT proved cytotoxic after just one dose. Maximum tolerated dosing research is currently underway.

BIO-DISTRIBUTION - IN VIVO

Preliminary studies on MGMR show no accumulation in lung, lymph, brain, and heart (Figure 3). Mouse lung from MGMR study (left) demonstrating no residual accumulation versus hyperspectral image of blood (right), where MGMR is seen as white and is evenly dispersed.

BIO-DISTRIBUTION - IN VITRO

MGMR has demonstrated intracellular penetration within minutes. MGMR distributes within the cell and naturally localizes in the nucleus, nucleoli, and the actin cytoskeleton (Figure 4).

TRANSDERMAL DRUG DELIVERY

MGMR was fully dispersed and polymerized into an ultrathin (1 to 5 microns) polymer-sheet, then coated onto a membrane support. Holes cut in the membrane support allow for the

FIGURE 2

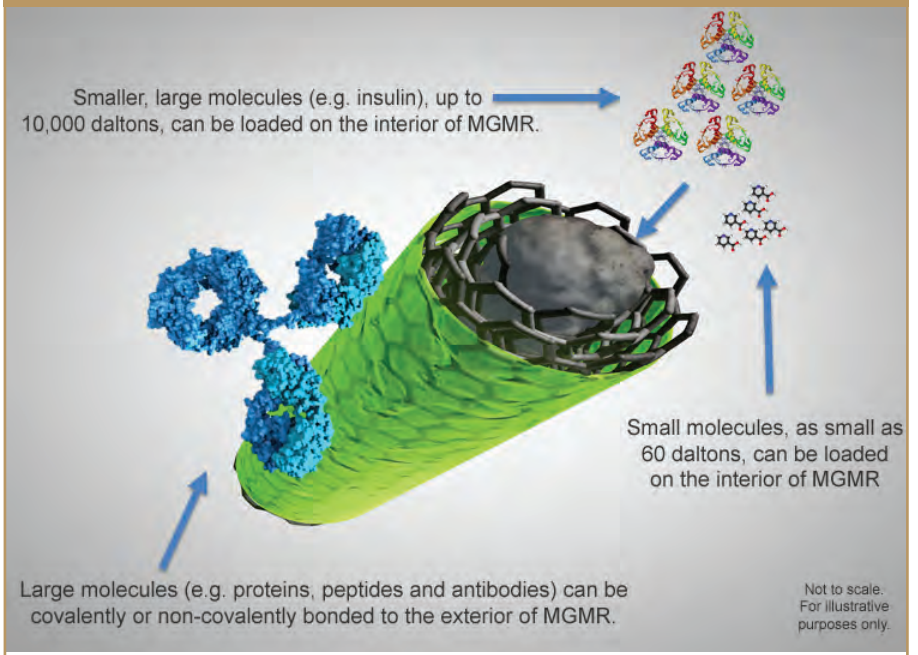


Illustration of MGMR: drug loading and binding

FIGURE 3

Mouse lung (left) hyperspectral image of blood (right)

visualization of the ultrathin transparent membrane loaded with fully dispersed MGMR. Free MGMR (not loaded) and MGMR filled with drug in ultrathin film have been dispersed. In three transdermal patch studies, no irritation, contact sensitization, cell lysis, or cytotoxicity was observed.

ACTIVE TARGETING - EX VIVO

MGMR can be preferentially targeted to the bone (Figure 5). The bright signal observed confirms MGMR targeting the bone using Fluorescent Microscopy.

CNTS: SCIENTIFIC ACHIEVEMENTS

Research using traditional CNTs in Alzheimer disease, Parkinson's disease, and numerous cancers demonstrates the future of engineering nanoparticles for drug and gene delivery to cells and tissues. With the introduction of MGMR, we can now apply this technology safely and more effectively to enable research in developing new drug delivery mechanisms. The following are a few examples.

Pancreatic Cancer - CNTs engineered as a nano-carrier for siRNA and drug delivery into pancreatic cancer cells.[1]

Brain Cancer (eg, GBM) - Uptake of CNTs into tumor combined with NIR photo thermal treatment ablates tumor (hyperthermia).[2] CNTs can transport chemotherapy drugs across the BBB and target drug payload to brain tumors.[3]

Blood Cancer (eg, Leukemia) - Daunorubicin-loaded MGMR can seek out and penetrate T cell leukemia cells.[4]

Breast Cancer - CNTs conjugated with paclitaxel (PTX) is expected to produce ten-fold higher PTX uptake by tumor.[5] See ablation procedure referenced previously, which also has application in the treatment of breast (and other) tumors.[6]

Colon Cancer - CNTs may be triple functionalized with an anticancer drug (eg, doxorubicin), a monoclonal antibody, and a fluorescent marker to enhance uptake of doxorubicin by the colon adenocarcinoma cell.[7]

FIGURE 4

Cytoplasmic and Nuclear Staining of Rhodamine-MGMR to a MCF-10A breast cancer cell

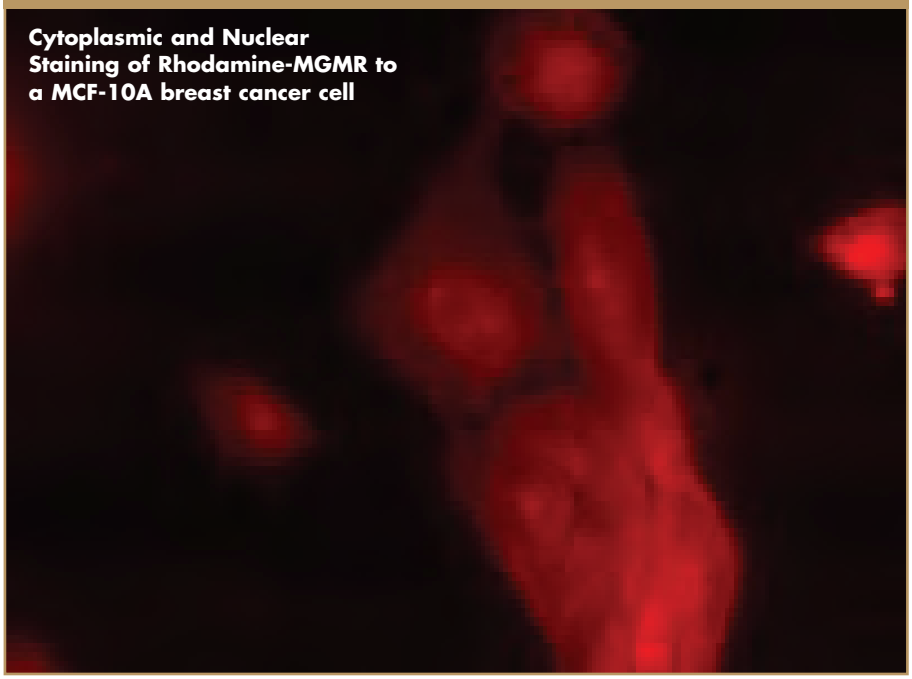
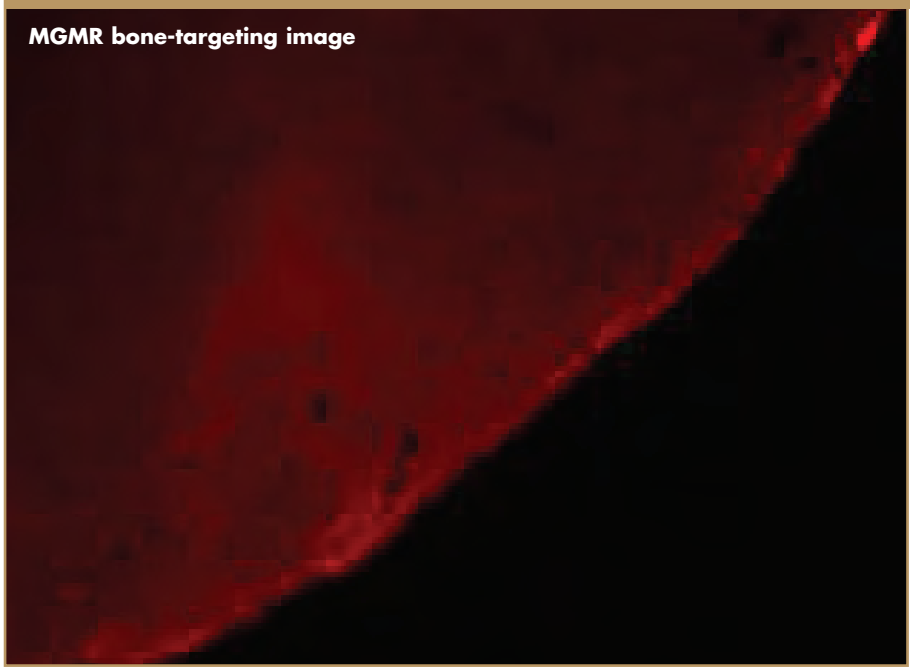


FIGURE 5

MGMR bone-targeting image



Liver Cancer - Dendrimer- modified CNTs may be engineered for the efficient delivery of antisense c-myc oligonucleotide (as ODN) into liver cancer cells, for maximal transfection efficiencies and inhibition effects on tumor cells.[8]

Lymph Node Metastasis - CNTs can be decorated with metallic particles, loaded with drug (eg, gemcitabine), and pass through a magnetic field for superior inhibition of lymph node metastasis and pancreatic cancer tumors.[9]

Prostate Cancer - CNTs conjugated with siRNA and a peptide, combined with the photothermal ablation therapy referenced previously can significantly enhance antitumor activity without causing toxicity to other organs.[10]

Crossing the BBB - CNTs can carry drug payloads across the blood brain barrier. Research has proven this based upon the drug crossing the barrier solely dependent on the physicochemical properties of CNTs, independent of the drug loaded inside.[11] MGMR shares these properties with the tested CNTs, while differentiating itself with safety data. Ritonavir (large molecule HIV drug) has been successfully transported across the BBB using TAT peptide - conjugated nanoparticles (many times the diameter of MGMR's 10- to 15-nm diameter) and delivered an 800-fold higher level of the drug in the brain when compared to free drug uptake.[11]

Nanoparticles averaging 150 to 200 nm in diameter (MGMR averages only 10 to 15 nm) conjugated with SynB peptide have been shown to be membrane-penetrable, cross the BBB, and deliver a drug to its target site in the brain.[12]

Alzheimer's Disease - CNTs may be safely used to deliver and control the dose of acetylcholine into the brain for treatment of Alzheimer's disease (in this study transport to the brain was via the olfactory nerve axons rather than across the BBB).[13] Uptake of Rivastigmine (used to treat dementia associated with Alzheimer's and Parkinson's disease) by the brain when transported by nanoparticles many times the diameter of MGMR (PnBCA) was almost 4x greater when compared to the free drug.[14,15]

Parkinson's Disease - Limited delivery of CNS of drugs, like L-Dopa (Levodopa), due to the BBB can be remedied by packing drug into CNTs, which can transport the drug across the BBB.[16] CNTs can evade the traditional degradation lines and target specific central nervous system structures which reduces systemic side effects.[16]

THE FUTURE OF MGMR

Medical Grade Molecular Rebar (MGMR) has the potential to make an impact on future research in a wide variety of applications, including but not limited to, autoimmune therapy, gene therapy, surgical implants, cancer therapies, CNS therapy and regenerative medicine. The potential to apply this technology to applications to develop a new product, resurrect a struggling development program, or to improve and extend the patented life of an existing product is available. Drug developers can resolve challenges in controlled release, targeted delivery, transdermal delivery, toxicity, and instability all with MGMR. Device developers can utilize MGMR's ability to be scaffolded, put into arrays, and utilize their highly conductive properties. ◆

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BIOGRAPHIES

Dr. Joseph S. Dillon is Chief Executive Officer of BioPact and brings over 2 decades of medical industry experience to the BioPact team. He is a seasoned executive with extensive experience in global pharmaceutical and biotechnology business strategy and planning, product development, operations, business development, and strategic transactions. Most recently, he was President & CEO of SynerPhysics, Inc. and President of Dillon Capital Strategies, a strategy and business analytics advisory firm. Prior to that, he held senior positions in pharmaceutical management consulting firms, most significantly was as Senior Vice President, Head of Corporate Development Services and Valuations for The Mattson Jack Group (now Kantar Health). Other previous positions include CEO, President, and Director of The Pharmaceutical Development Center, Executive Vice President and CFO of Vail Banks Inc., CFO and Treasurer of Oread Inc., and corporate positions with predecessor companies of Sanofi. He is Past-Chairperson of the Licensing Executive Society Life Sciences Sector. Dr. Dillon earned his PhD in Metaphysics, his MBA in International Finance, and his BA in Finance.

Lainie Mulvanny is the VP of Business Development at BioPact. She is focused on corporate and academic collaborations to develop MGMR-enabled products for medical use. She is responsible for the assessment of unmet needs in the drug delivery space and the development of strategies for BioPact's partnering-focused development model. Her medical industry experience includes positions at Sanofi-Genzyme, Merck, and Ciba Vison. She earned her BA from California State University, Pomona. She can be reached at lainiem@bio-pact.com.

PROTEIN CRYSTALS

Reshaping Traditional Biotherapeutic Formulations

By: Don Paul Kovarcik, MBA, and William Wittbold, MS

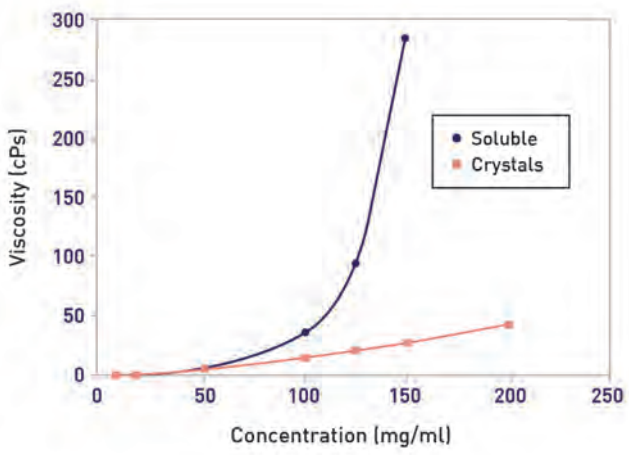
INTRODUCTION

Throughout the past decade, protein-based therapeutics have emerged as the key driver of growth in the pharmaceutical industry. R&D pipelines have filled with more and more biologics and, in recent years, monoclonal antibodies have become the fastest growing segment of biological drugs around the world. Despite the success of this segment, there are specific challenges to overcome when developing these types of therapeutics. Unlike small molecules, protein-based therapeutics are almost exclusively administered by parenteral routes.[1] Because of the size, biochemical complexity, and low bioavailability of these macromolecules, high doses must also be administered. At high concentrations, protein-protein interactions significantly increase solution viscosities and may result in the formation of aggregates. This in turn decreases manufacturability and complicates drug delivery.[2,3] Moreover, aggregates are of special concern because they have been shown to be associated with altered biological activity and increased immunogenicity.[4-7] Currently, most protein-based biologics are administered via larger volume, lower concentration formulations via intravenous (IV) infusion. However, these procedures are less patient-friendly, more costly, require trained medical professionals, and often involve a visit to a clinic.

OVERCOMING CHALLENGES WITH CRYSTAL FORMULATIONS

From a cost and patient compliance perspective, subcutaneous injection (SCI) would be the preferred route of administration. To keep patient discomfort to a minimum, SCI volumes generally do not exceed 2 milliliters. The high dose necessary for clinical benefit raises concerns about the

FIGURE 1



The viscosity of soluble and crystalline suspensions of Infliximab. Infliximab is a monoclonal antibody against tumor necrosis factor alpha (TNF-α). It is marketed under the trade names Remicade® (Janssen Biotech), Remsima™ (Celltrion), and Inflectra™ (Hospira) for the treatment of Crohn's disease, psoriasis, and other autoimmune diseases. Viscosity was measured using a Cannon-Fenske viscometer according to the manufacturer's instructions. It should also be noted that small gauge needles can accommodate viscosities up to about 20 cPs.

exponential relationship between protein concentration and viscosity.[8] High viscosity levels reduce syringeability (loading) and injectability (delivery to patient). It has been demonstrated that highly concentrated crystalline suspensions do not result in a similar increase in viscosity (Figure 1).

The viscosity of a suspension (η) is primarily determined by viscosity of the formulation vehicle (η_0) and the suspension viscosity is dependent on the crystal volume fraction (Φ) (Figure 2).

FIGURE 2

$$\eta = \eta_0(1+2.5\phi)$$

Einstein equation for suspensions.

Because protein crystals are highly organized, tightly packed structures (Figure 3), their volume fraction is considerably less than an equivalent number of protein molecules in solution. The advantages of protein crystals aren't just limited to lower viscosity.

Proteins are complex macromolecules that require a specific three-dimensional structure in order to be biologically active. The interactions that drive and stabilize higher order secondary, tertiary, and quaternary structures are inherently weak and mainly driven by hydrophobic interactions but also stabilized by hydrogen bonds, salt bridges, and disulfide bonds. As a result, proteins are susceptible to physical or conformational degradation. A number of external factors can cause physical degradation, including higher temperatures, pH, mechanical agitation, and high shear forces to name a few. Crystals present a uniquely stable form of proteins and help protect against many forms of degradation. Moreover, studies have shown that the crystallization process does not affect the biological activity of a protein (Figure 4).

Crystal formulations have long been used for long-acting versions of small molecule drugs. Crystal formulations of therapeutic proteins can also be used to develop products with extended-release properties. Crystal Infliximab administered monthly has the same effect as the soluble form administered weekly in a TNF-α mouse model (Figure 5).

Due to improved handling, increased stability and the possibility of controlled release, crystal formulations of small molecule therapeutics have been on the market for decades.[9] However, to date, insulin is the only biologic available in a crystal formulation. What then are the key issues that are preventing the widespread development of these advantageous formulations?

CHALLENGES OF DEVELOPING A CRYSTAL SUSPENSION FORMULATION

There are two main challenges to developing a crystal suspension formulation. The first is to the find a robust crystallization condition that will produce crystals within a short period of time – sufficiently short for GMP manufacturing, preferably less than 24 hours. The second challenge is the development of a drug product formulation that is suitable for injection while maintaining stability in the crystal structure. Finding conditions in which a protein crystallizes is the initial challenge, and oftentimes those crystallization conditions have properties that are not suitable for introduction into patients, ie, non-Generally Regarded As Safe (GRAS) excipients, not isotonic, etc. The second, and often more difficult challenge is then to reformulate the crystal suspension into excipients suitable for injection that also maintain crystal integrity and molecular function upon dissolution.

GMP MANUFACTURING OF THERAPEUTIC CRYSTAL FORMULATIONS

Proteins have been crystallized for structural studies in biochemistry laboratories for over 50 years. However, the requirements of and methods for producing protein crystals for therapeutic purposes are significantly different. Most crystallographers want a single large

FIGURE 3

Crystal Size (μm)	0.1	1	10	100
Number of Protein Molecules	10^4	10^7	10^{10}	10^{13}

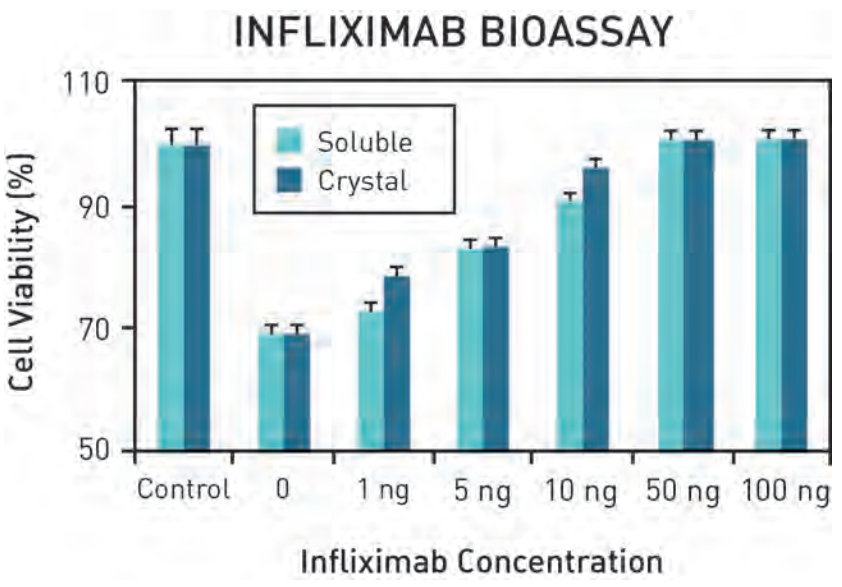
Crystal size as a function of the number of protein molecules.

size crystal (> mm) for structure studies, whereas formulation scientists want very high concentrations of uniform crystals (> 200 mg/mL) that are several orders of magnitude smaller, typically 5 to 30 µm. Protein aggregation is a concern during crystallization - if precipitant amounts are too high, then the individual protein molecules assemble too rapidly and not in order resulting in aggregation. A lot of time and effort is invested in finding the optimal balance to regulate crystal assembly and growth without aggregation.

In addition, the ideal crystallization conditions change as the project moves from vapor diffusion screening to micro-batch screening. Conditions that work at the 3-µl level usually don't translate well to the 15-µl level. Scaling the volume of the crystallization reaction affects how the crystals form. In early development (volumes < 3 µL), evaporation is the primary driver for crystallization. As water evaporates from the small drop, the concentration of excipients increases until crystals form (if conditions are right). In larger volume reactions (> 15 µL and up), there is insufficient surface area for evaporation to be the main driving force behind crystallization. By this point, however, optimization efforts likely have determined the conditions that don't rely on evaporation to produce crystals with the desired properties. To scale further, it is necessary to move into tank systems (50 mL and up). Tank systems, because of their significantly larger volumes, introduce additional variables that can affect crystal yields and quality; these variables include mixing rate, impeller design, order of excipient addition, and temperature.

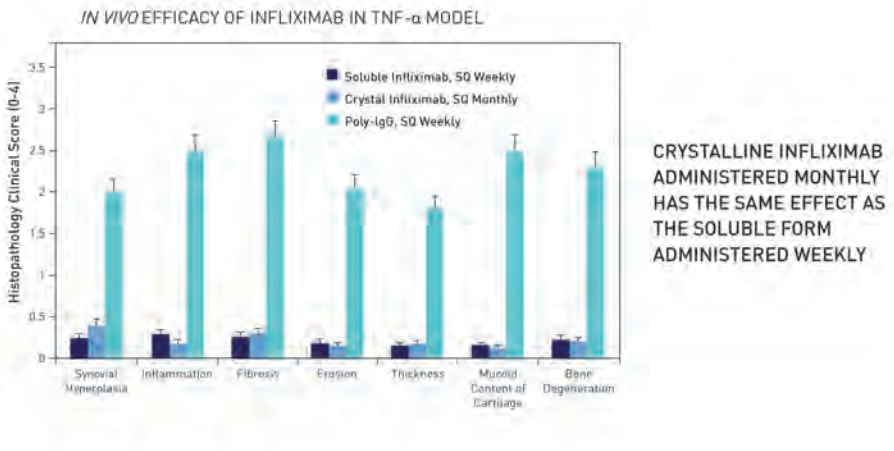
Following the discovery of the optimal crystallization conditions, the next step is formulation development. This can be as challenging as developing the optimal crystallization process. Even when a robust process to make small (10 mL) batches of uniform crystals has been developed, the excipients are typically not GRAS. Often, the protein crystals need to be reformulated into GRAS excipients suitable for subcutaneous injection that are also in the desired pH, osmolality

FIGURE 4



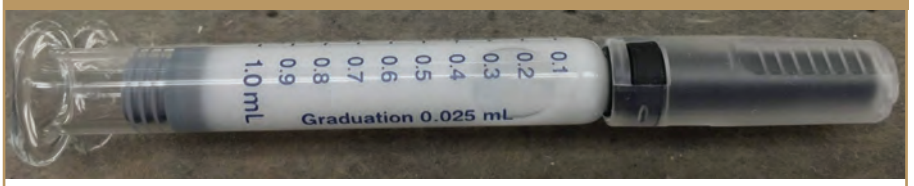
Cultured L-929 mouse fibroblast cells were detached, diluted to 2x105 cells per mL and added to 96-well plates (100 µL per well). TNF-α neutralization assays were performed by incubating mouse fibroblast cells overnight in the presence of 100 pg/mL TNF-α and various concentrations of Infliximab or dissolved crystals of Infliximab. The number of viable cells was determined by using a commercially available cell proliferation assay kit.

FIGURE 5



Approximately 100 µL of Infliximab (20 mg/mL) was subcutaneously administered to C57BL/6NTac-TgN(TNF- α) mice at a dose of 8 mg/kg in both soluble (weekly) and crystallized (monthly) forms. Non-specific IgG was used a control.

FIGURE 6



Syringe filled with a crystalline suspension of recombinant human growth hormone.

range, and break loose energy (BLE - how much force is needed to expel the material from a syringe).

Downstream purification of the desired crystal size can be a challenge. Even with the tightest controls, in each batch, there will be distribution of various crystal size populations. Centrifugation can be used to purify; however, it is not a preferred method. Centrifuge bottles can shed particles thus contaminating the crystals. It's possible to pre-clean and irradiate the bottles prior to centrifugation, but this adds additional steps to the process. In addition, operators have to manually handle and pour to/from the bottles, introducing risk of spills, errors, and contamination. A better option would be an automated, closed system such as tangential flow filtration (TFF). It reduces the chance for human error, is gentler, and reduces the risk of contamination when compared to centrifugation.

The next steps in the process are fill finish manufacturing, release testing, and visual inspection. There are two major areas of concern when filling crystalline therapeutics: suspension uniformity and fill weight accuracy. In addition to the typical release assays for a protein-based biologic, it's also important to perform extensive dissolution and biophysical characterization studies of the API pre- and post-crystallization to show protein isn't affected by the crystallization process or the crystals themselves. The final step is manual visual inspection. Manual visual inspection is the standard in both the US and Europe and heavily relies on the experience, training, and skill of the operator. Specialized training is needed to identify the potential defects in opaque crystalline suspensions that resemble a milky fluid (Figure 6).

THE SOLUTION – ALTHEA'S CRYSTALOMICS® FORMULATION TECHNOLOGY

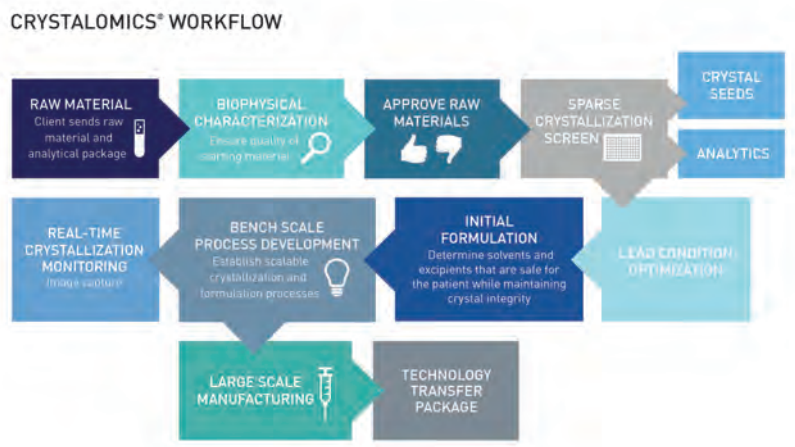
To help clients develop crystalline formulations, Althea offers access to a proprietary Crystalomics® Formulation Technology. Althea's unique portfolio of intellectual property encompasses crystallization, cross-linking, and complexation of proteins for therapeutic use. It includes patents, proprietary knowledge, and expertise to develop ideal crystallization conditions, stable crystalline formulations, and scale-up for GMP manufacturing of crystalline suspension drug products. The technology allows companies to produce highly concentrated formulations with low viscosity, enabling low-volume doses and increased stability. The resulting crystalline suspensions are easier to administer and offer the chance to extend the patent life of high-value biologic drugs. A typical crystallization workflow conducted at Althea is shown in Figure 7.

Althea has been successful developing crystallization conditions and stable crystal suspension formulations for over 100 molecules, including antibodies, hormones, enzymes, and peptides from human, animal, and microbial sources.

SUMMARY

While protein therapeutics have enjoyed considerable commercial success throughout the past 3 decades,

FIGURE 7



A workflow diagram of a typical crystallization project.

TABLE 1

Benefits of Crystal Formulations	
Pharmaceutical Developers	**Patients**
Ability to formulate highly concentrated proteins in small injection volumes	Better compliance without time-consuming IV infusions
Scalable to support both clinical stage and commercial manufacturing	Self-injection that doesn't require trained medical personnel
Maintains biochemical characteristics and bioactivity of the soluble protein	Improved patient comfort via use of finer gauge needles
Improvement in syringeability and injectability	Non-injection routes of administration possible
Flexibility in dosage form–oral, pulmonary, topical and subcutaneous injection possible	Fewer treatments via controlled and extended release formulations
Opportunity to extend patent life of branded protein-based therapeutics	Same therapeutic benefits as low concentration formulations

Summary of the benefits of protein crystal formulations.

there still remain formulation and delivery challenges. Due to poor bioavailability and unfavorable pharmacokinetics, frequent administration of large doses is often necessary for clinical benefit. Highly concentrated solutions usually have high viscosity resulting in poor syringeability and injectability. Out of necessity, these products are formulated as low concentration solutions that have to be administered as large volume IV infusions. IV infusions are more expensive, time-consuming, and have to be administered by trained medical professionals. Protein crystals have shown potential to address these issues and can benefit both pharmaceutical developers and patients (Table 1).◆

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BIOGRAPHIES

Don Paul Kovarcik is the Technical Marketing Specialist at Ajinomoto Althea, Inc. He is responsible for developing technical marketing pieces for all aspects of Althea's business, including drug product (fill finish) manufacturing, drug substance manufacturing, Crystalomics® Formulation Technology, and Corynex® Protein Expression System. Prior to joining Althea, he worked in a variety of marketing and business development roles at Lonza in their research products and cell therapy contract manufacturing business units; specifically focused on the development of pluripotent stem cell product and service offerings. He earned his BS in Biochemistry from Virginia Tech and his MBA from Carnegie Mellon University.

William Wittbold is the Manager for Crystalomics® Technology Transfer at Ajinomoto Althea, Inc. After earning his BS and MS in Microbiology from the University of Massachusetts Amherst, he worked in positions with InfiMed Therapeutics, University of Massachusetts Medical School, Altus Pharmaceuticals and Wyatt Technology. With an extensive background in protein crystallization, biophysical characterization, and assay development, he guides client and internal projects from screening through GMP manufacturing and fill finish. He has diverse experience working with clients ranging from startups to large pharmaceutical companies.

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Special Feature

Excipients: Manufacturers Look to Co-Processing as a Way of Improving Functionality

By: Cindy H. Dubin, Contributor

Sucrose, courtesy of Pfanstiehl.

The global excipients market should reach nearly $6.9 billion by 2020 from approximately $6.3 billion in 2015, according to a new report from BCC Research, LLC. Growth in the demand for pharmaceuticals and biopharmaceuticals should drive market growth in the excipients market as will the development of innovative drugs for chronic diseases and an increase in generic drug production. Increased research and development spending, growing competition, looming patent expiries, new technologies, and upcoming product launches are key market drivers, as well.

While there is a need for new excipients to increase options for the formulation and delivery of the newer molecules coming through the development pipelines, few new excipients have reached the market due to high development costs and stringent regulatory requirements, according to the report. Thus, developing new excipients requires expensive and time-consuming safety evaluations. As a result, some manufacturers are concentrating on co-processing existing approved excipients. Innovative co-processed excipients, or excipient composites, are being engineered to achieve the properties of key components of the tableting blend in a single, highly flowable and compressible granular material.

"With the increasing development of new chemical entities, there is a huge opportunity for the development of co-processed excipients, and development of such innovative co-processed excipients with multi-functionality is beneficial for the market," says BCC Research Analyst Shalini S. Dewan.

In this exclusive *Drug Development & Delivery* report, we uncover how leading excipient manufacturers are overcoming their own R&D challenges to deliver innovative excipients that address problems associated with both large and small molecules.

ABITEC—Functional Lipids for Injectable Delivery

The majority of new chemical entities (NCEs) being considered as active pharmaceutical ingredients (APIs) are poorly water soluble. Lipid Based Drug Delivery (LBDD) employing functional lipids is one of the most effective means to overcome solubility challenges for BCS Class II and Class IV APIs, says John K. Tillotson, RPh, PhD, Pharmaceutical Technical Business Director (Americas), ABITEC.

Functional lipids offer many advantages including: complete dissolution of the API in the lipid; dispersion of the dissolved API in the GI tract in the form of API-containing micelles; resistance to API precipitation; protection from enzymatic degradation; and adaptive chemistry allowing for the selective synthesis and application of lipid systems specific to respective API characteristics.

LBDDs are formulated by dissolving the API in a neat lipid or in a combination of lipids and surfactants to formulate a pre-concentrate. When the API is dissolved in a neat lipid, the API-containing lipid is digested by bile salts and digestive enzymes to form an API-containing emulsion, which is then absorbed. When the API is dissolved in a combination of lipids and surfactants, the pre-concentrate generates an emulsion upon contact with the fluid in the GI tract. The API-containing emulsion is subsequently absorbed.

"A recent ABITEC innovation, the INJECTA™ line, brings the dissolving power of ABITEC's highly functional lipids to injectable applications," says Dr. Tillotson.

The INJECTA line includes Captex® triglycerides and Capmul® mono- and di-glycerides manufactured specifically for injectable formulations. The INJECTA products can be employed in a range of applications, including injectable, transdermal, and ophthalmic formulations. INJECTA products are monograph compliant and are tested for endotoxins, heavy metals, and microbes.

Ashland—Polymers Address Complex Chemical Entities for Oral Delivery

A cornerstone of Ashland's excipient technology development program is the need to enhance the bioavailability of difficult-to-deliver

drug molecules formulated for oral routes of administration. Today, the company is investing in the advancement of existing polymer technology, while designing new polymers with the potential to significantly improve the solubility and permeability of chemical entities with complex biopharmaceutical and physical-chemical properties, explains Thomas Durig, PhD, RPh, Senior Director, Pharmaceutical and Nutrition Specialties R&D, Ashland. These troublesome NCEs reside in two main groups: molecules that tend to form strong crystalline structures and those that tend to be highly lipophilic in nature. "Ashland is helping pharmaceutical companies to advance these NCEs by improving the mechanistic understanding of amorphous solid-dispersion technology," says Dr. Durig. "This expertise is applied in the development of new polymeric delivery technologies to facilitate more predictable and dependable *in vivo* drug delivery performance."

In addition to challenging NCEs, there are challenges associated with developing co-processed excipients in that there are few blends that fulfill the formulating requirements of a large number of drug molecules. "Although co-processing can be a viable route to a functional excipient that provides superior flow and direct compression tableting, with best-in-class controlled release, generally, the range of large-volume co-processed excipients will be limited," says Dr. Durig. "One success is Ashland's new series of Benecel™ hypromellose (HPMC) grades for controlled-release matrix tablets." Ashland will present the results of new highly functional developmental grades of hypromellose acetate succinate (HPMCAS) at the 2016 Controlled Release Society. Following additional studies and peer review, these excipients are expected to be available as commercial products.

In addition to co-processing excipients, Ashland is interested in co-development. According to Dr. Durig, development of novel excipients continues to be a challenge in that there are no approval processes in place for such technologies. "The poor bioavailability and other hurdles in small-molecule development have made pharmaceutical companies more open to co-developing new excipients because some bioavailability issues cannot be resolved with existing excipient technology. For example, more companies view co-development as a potential process to rescue therapeutically viable drugs that cannot otherwise come to market. It is for this reason that Ashland is willing to invest in new technology and provide expertise about these technologies to help companies solve major problems."

Ashland is also investing in ways to comply with the directives of Quality by Design (QbD) and reduce risk to the supply chain. Ashland has product safety and quality management systems to meet a range of regulatory requirements for all excipients. In February 2016, Ashland's manufacturing plant in Calvert City, KY, received EXCiPACT certification for Good Manufacturing Practices (GMP).

Evonik—Tool Identifies Appropriate Combinations of Polymers

For bioavailability and solubility enhancement of poorly soluble actives in oral formulations, rather than developing exotic new unapproved polymers giving rise to regulatory issues, Evonik has developed a versatile tool called MemFis™ (Melt Extrusion Modeling and Formulation

Evonik manufactures methacrylate copolymers under the EUDRAGIT® tradename.

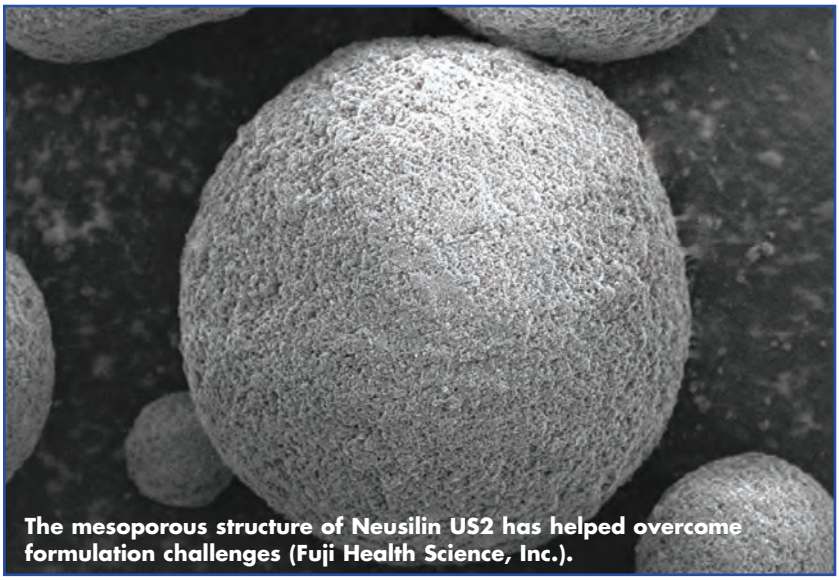
Information System) to identify appropriate combinations of existing and approved pharmaceutical-grade polymers with the API of interest to form stable solid solutions, explains Dr. Firouz Asgarzadeh, Director Technical Services, Pharma Polymers and Services, Health Care, Evonik.

Evonik has used MemFis for screening polymers suitable for solubility enhancement of poorly soluble actives. With this tool, all approved IIG-listed polymers are considered for the development of solubility-enhanced APIs utilizing spray-dried dispersion (SDD) and hot-melt extrusion (HME) techniques.

One pharma client had developed an HME product with a contract research organization (CRO) where the development was carried out by the arbitrary selection of polymers rather than taking into account functional and structural considerations. This client heard about MemFis and decided to try the tool. MemFis identified a previously overlooked polymer as the most compatible for the API under development. The actual dissolution results confirmed that the selected polymer provided the best solubility enhancement allowing for a successful formulation change for animal studies.

This year, Evonik will launch a 100% solids version of an existing aqueous anionic polymer that has proven to be highly suitable for HME and SDD approaches.

Evonik has already launched several combinations of excipients in partnership with other experts in the field, including, but not limited to, Acryl-EZE® (a Colorcon product), which is a ready-to-use enteric excipient based on EUDRAGIT® L100-55, EUDRAGIT® EPO ReadyMix for taste-masking/moisture protection, and PlasACRL® (a product of Emerson Resources), which is a ready-to-use emulsified plasticizing system for enteric and sustained-release coating systems.



The mesoporous structure of Neusilin US2 has helped overcome formulation challenges (Fuji Health Science, Inc.).

"Co-processed APIs may be the future of pharmaceutical discoveries," says Dr. Asgarzadeh. "Currently, when developing new APIs, there is a large amount of research done to identify the most crystalline forms. The highly crystalline drugs are very difficult to solubilize in the aqueous conditions of the gastrointestinal tract, which leads to the development of solid solutions to change the active structure back into an amorphous form in a higher state of energy to improve solubility of these compounds. Utilizing polymers during manufacturing of actives in a co-processed system may potentially allow for the stabilization of the amorphous state of the active in a matrix structure, thus avoiding additional processing and overcoming the solubility issues."

Fuji Health Science, Inc.—Solving Production & Incompatibility Issues

Excipient manufacturers, like Fuji Health Science, Inc., are focused on developing problem-solving excipients to overcome the new challenges that arise from new investigational drugs and novel drug delivery systems.

For example, a client of Fuji's was experiencing production issues with a roller compaction process. Conventional Dibasic Calcium Phosphate Anhydrous (DCPA) was in the formulation, which was causing poor flow and compressibility, explains Xi Han, PhD, Fuji Health Science, Inc. "When the client tried Fuji's DCPA-Fujicalin®, powder flow and compressibility were significantly

"Although co-processing can be a viable route to a functional excipient that provides superior flow and direct compression tableting, with best-in-class controlled release, generally, the range of large-volume co-processed excipients will be limited."

improved. This is because Fujicalin is made through a proprietary spray drying technology, resulting in superior flow and compressibility. By using Fujicalin in the formulation, the client was able to resolve the manufacturing issues."

As another example, a customer was looking for an alternate dosage form for a lipid-based delivery system. Initial trials with a liquid-filled softgel had failures in stability due to an incompatibility between the drug and capsule shell. "Various carriers were evaluated to solidize the lipid and Fuji's excipient Neusilin® (mesoporous Magnesium Aluminometasilicate) was determined to offer the best performance in terms of drug loading, dissolution, and tablet hardness without the need for additional binders," says Dr. Han.

Gattefossé—New Excipient With Micellar Capacity for Solid Dosage Forms

Addressing drug delivery challenges with innovative excipients has been a core specialty of Gattefossé. Its products are widely applied in oral, topical, transdermal, injectable, and mucosal delivery, and include solubility/bioavailability enhancers, sustained-release matrix formers, and skin penetration/permeation enhancers.

Gattefossé supports each excipient with clinical safety data, regulatory files, physicochemical characterization, and analytical methods. The excipient applications are equally supported with guidance documents for formulation design, decision trees, and current evaluation methods. In addition, Gattefossé offers preclinical guidelines for the preparation and dosing of lipid-based formulations, explains Jasmine Musakhanian, Scientific and Marketing Director, Pharmaceutical Division, Gattefossé USA.

Among Gattefossé excipients, the newly launched Gelucire® 48/16 keeps the drug in a solubilized state by forming micellar solutions upon contact with aqueous media. This micellar capacity is easily maintained throughout dilutions and digestive processes that convert its diesters to monoesters, replenishing the micellar system that holds the drug in solution until it reaches the enterocytes. An additional and important characteristic of Gelucire 48/16 is its solid state behavior, which makes its handling very easy and facilitates formulation of solid dosage forms. Gelucire 48/16 not only exhibits solubilization capacity *in vitro* and *in vivo*, but also has processing advantages for preparing solid dosage forms.

Pfanstiehl—Stabilizing Molecules for Parenteral Delivery

Pfanstiehl's focus is on high quality cGMP manufacturing of injectable/parenteral-grade excipients like trehalose, sucrose, mannitol, and maltose for use in stabilizing formulations for monoclonal antibodies, antibody drug conjugates (ADCs), vaccines, small molecules, and cell-based therapies.

"As the demand for increasingly complex therapeutics, such as mAbs and ADCs, continues to grow, so does the need for high purity, low endotoxin excipients that effectively improve the yield and stability of these high value actives," says Chris Wilcox, PhD, Vice President, Business Development, Technology Specialist, Pfanstiehl, Inc.

One key area of focus for Pfanstiehl is on redefining its understanding of the minor constituents of its excipients and the impact they have on customers' formulations. These include key quality attributes such as endotoxin, total impurities, elemental impurities,

and sub-visible particulates.

"Being able to quantify levels of impurities well below those required by the pharmacopeia, so that we can be a true solution partner for our customers and build further robustness into our manufacturing processes, is a high priority for us," Dr. Wilcox says. "Each year, we see the gap in quality/regulatory expectations between APIs and excipients closing. As a CDMO for APIs, we understand the implications of this trend and are working to ensure that our customers have peace of mind when it comes to use of these critical excipients in formulations that may have development and commercial lifecycles of 30 years or more."

Pfanstiehl also ensures peace of mind through its raw material qualification activities. Pfanstiehl has invested significant resources toward enhanced characterization of raw materials and the final excipient products in order to facilitate qualification activities. As an example, Pfanstiehl's program of quantitative elemental impurity characterization down to ppb levels recently enabled one of its clients to de-risk its supply chain by qualifying one of Pfanstiehl's excipients manufactured from multiple raw material sources. "By providing very detailed data from our end, our client was able to demonstrate that the impact on the final formulation was negligible," explains Dr. Wilcox. "As a result, the client now has peace of mind that the risk associated with sourcing this excipient for the long term is very low."

The SPI Pharma Pharmaburst® ODT platform is a co-processed excipient for improved functionality.

High purity, low endotoxin excipients like trehalose, sucrose, and L-Arginine have long been utilized in parenteral dosage forms for stabilizing monoclonal antibodies and other protein-based therapeutics. "Increasingly, we find that these same excipients are being used not just in final formulation but in downstream purification to increase solubility of proteins and improve yield," says Dr. Wilcox. "This is believed to result from the inherent ability of these excipient molecules to prevent aggregation, essentially acting as chaperones for the proteins, shepherding them through the gauntlet of downstream process steps, limiting undesirable protein-protein interactions, and ultimately improving product quality and process efficiency."

SPI Pharma—Co-Processed Excipients Optimize Functionality

SPI Pharma provides functional excipients and active ingredients to solve formulation problems, achieve differentiation, and gain speed to market. Its primary focus is functionality, such as superior compactability, increased solubility, and improved stability. This has been achieved through co-processing select sets of excipients to derive functional synergy. An example is its patented Pharmaburst® ODT platform, which is a co-processed excipient system to gain specific functionality.

"Co-processed excipients are specifically designed to provide value-added performance that cannot be obtained by simply blending the components," says Sarath Chandar, EVP Licensing & Technology, SPI Pharma. "This is often accomplished through particle engineering where one or more compendial ingredients are combined at the particle level."

A major advantage of co-processed excipients, he says, is that products with greater functionality can be obtained without developing a new chemical compound. Approval of a new chemical compound would

Suglets® Sugar Spheres (Colorcon).

require a lengthy regulatory approval process for safety and toxicity issues.

Another advantage is convenience and efficiency. Fewer ingredients are needed for formulation and manufacturing, so fewer raw materials need to be tested, handled, and inventoried. "The entire process can be streamlined, resulting in lower costs. And, because fewer materials are used, there is less variability, simplifying quality by design," he says.

SPI Pharma has developed several co-processed excipients with optimized functionality for orally disintegrating tablets and granules as well as soft chew tablets. These products are fully formulated to provide rapid disintegration and superior organoleptic characteristics while producing dosage forms that are robust enough to stand up to handling and packaging, he says.

"With the introduction of the Pharmaburst ODT platform as the first off-the-shelf, directly compressible ODT platform, SPI Pharma has helped global customers launch about 45 new ODT products with both Rx and OTC APIs, some of them achieving Para IV status in the US market," says Mr. Chandar.

Colorcon—Getting to the Core of Multiparticulate Quality

Colorcon supplies pharmaceutical excipients and coatings. Its particular expertise in coatings led the company to explore how sugar spheres, as an inert carrier for drug loading, can impact drug release.

"Our customers have requested support to troubleshoot inconsistent dissolution profiles when using modified-release coatings on multiparticulates," says Mike Gilbert, Market Development Director, Colorcon Inc. "Through working on these projects, we discovered that the inconsistency of the sugar beads could affect the robustness of the coating."

Variability in size directly affects the thickness of the applied coating, and, therefore, the diffusion and dissolution performance. Friability of the substrate can impact size and smoothness of the bead, affecting coating thickness and dissolution performance. "While monographs specify targets for various properties, we have seen that often these tests have no influence on the performance of the final product," says Mr. Gilbert.

For example, the current USP monograph for sugar spheres includes particle size distribution by sieve analysis, which does not account for any differences in particle shape or sphericity. However, these factors can greatly influence the efficacy of a drug layering or modified-release coating.

"Colorcon utilizes advanced particle size analysis using dynamic imaging analysis to capture true size, shape, and sphericity of individual sugar spheres," says Mr. Gilbert. "We have set internal specifications exceeding monograph requirements to ensure a more consistent finished product."

Historical trending analysis of these critical properties is available and reviewed by Colorcon operators and quality assurance teams, and this data is made available to customers.

Colorcon has two Suglets manufacturing locations in Stoughton, WI, and Bazainville, France. Mr. Gilbert says Colorcon is the only pharmaceutically focused sugar sphere manufacturer with the ability to produce the same product out of multiple sites. ◆

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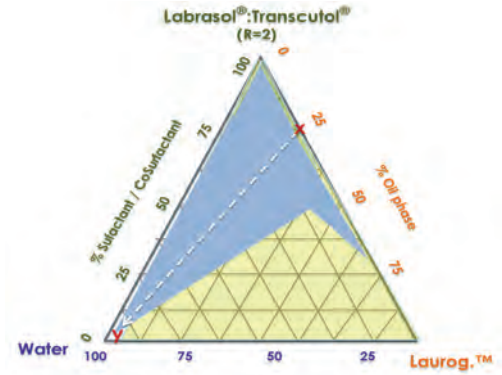
Formulation Development



Ternary diagramming is an indispensable tool for developing microemulsions and SMEDDS for topical or oral delivery of poorly soluble drugs. In this example, the blue zone represents unlimited number of formulations possible by simply varying combinations of three excipients. Point "X" for instance is SMEDDS containing 25% Lauroglycol™ +75% mixture of Labrasol®: Transcutol® (2:1). Continuously adding water to formulation "X", we would be following the dilution path along the white arrow. In other words, the formulation "X" may be diluted with no risk of phase separation as it will remain a nano-dispersion even at a very diluted state. Designing SMEDDS and Microemulsions binary and ternary diagramming is a Gattefossé expertise. For more information, please contact **jmusakhanian@gattefossecorp.com.**

Automated Delivery System

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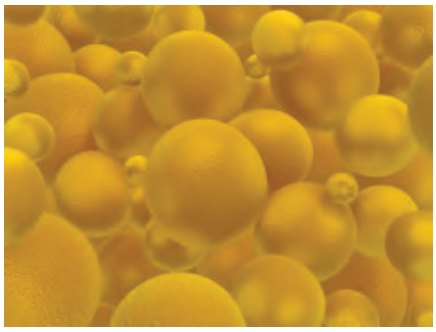
Technology & Services Showcase

Nanoemulsion Formulations



Ascendia Pharmaceuticals offers services for contract formulation development of poorly soluble drugs. Our formulation approaches include nanoemulsions, amorphous solid dispersions, and nanoparticles. These technologies are suitable for oral or injectable delivery of drugs that are challenging to formulate. EmulSol is our technology for production of oil-in-water nanoemulsions, with droplet sizes in the range of 50-500 nanometers. Ascendia's process is novel in that it uses no organic co-solvents, and minimal surfactants. Our nanoemulsions use a high-shear homogenization process to create a suspension of the oil droplets in a water phase, with the drug solubilized within the interior of the oil droplets. Thus, when the nanoemulsion is delivered to the body, the drug is more readily bioavailable. For more information, contact Ascendia at (732) 640-0058 or visit **www.ascendiapharma.com.**

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Technology & Services Showcase

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Drug Development
EXECUTIVE

Jean Pierre Wery
President
Crown Bioscience

Crown Bioscience: Enhancing the Drug Development Process

Crown Bioscience, Inc. is a preclinical CRO with expertise in the disease areas of oncology and metabolic disease. The company is known for the breadth and quality of its in vitro and in vivo models, as well as its ability to help clients quantify the real efficacy and pharmacological profile of their candidate before they move into the clinic. As drug discovery continues to rapidly evolve, there is a growing need to screen candidates earlier and with more patient-relevant models, which more closely reflect the situation in the clinic and therefore help improve the selection of drug candidates. Crown's unique collection of ready-to-run, well-validated in vitro and in vivo models, expertise in model development, comprehensive drug discovery platforms, and global capacity enable them to deliver the results their clients need. *Drug Development & Delivery* recently interviewed Jean Pierre Wery, President of Crown Bioscience, to discuss the requirement for more accurate research models in oncology research, focusing on patient-derived xenograft (PDX) models that have the ability to more adequately represent the conditions and mechanisms of immunotherapy in human patients.

Q: For our readers who may not yet be familiar with your company, can you briefly discuss Crown Bioscience and what it offers?

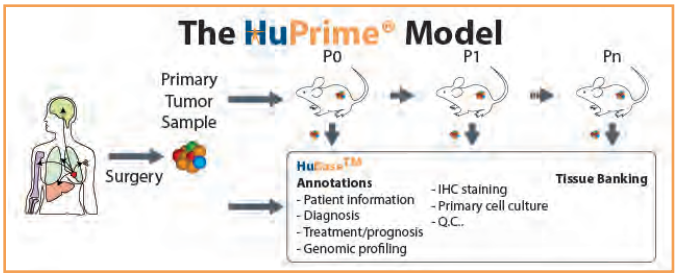
A: Since 2006, Crown Bioscience has been building and developing a portfolio of unique resources to help our clients in their endeavors to bring improvements in patient outcomes. Our mission is to address the unmet needs of life sciences by creating and supplying innovative translational technologies and platforms. Our products and services have been profoundly expediting research for in vitro, in vivo, translational oncology, target validation, preclinical proof-of-concept, assistive clinical strategy design, and biomarker discovery.

Our comprehensive drug discovery services and unique portfolio of models for both oncology and metabolic diseases enable our customers to significantly accelerate and improve the quality of their decision-making process about which candidates to move into the clinic. As a preclinical CRO, we provide a unique range of models and services to help our clients accelerate their research and drug development efforts.

Crown's fully integrated drug discovery capabilities increase the speed and efficiency of progressing hits to preclinical candidates. Our disease expertise and innovative translational research platforms enable our clients to successfully identify their most robust molecules and determine strategic therapeutic areas and indications to enhance success in Phase II & III clinical trials.

Q: What products and services does Crown Bioscience specialize in?

A: Crown Bioscience has an array of products, including antibodies, cell lines, and tumor samples, and we specialize in preclinical mouse models. We have developed the world's largest commercial collection of Patient Derived Xenograft (PDX) models (HuPrime®), assays, and annotated databases (HuBase™, XenoBase™, and MuBase™) that our clients can use to conduct exhaustive evaluation of compound efficacy. With our well-characterized PDX models, we can conduct preclinical Phase II-like trials - HuTrial™ - to discover and evaluate predictive biomarkers before a single patient has been dosed.



The majority of HuPrime models are maintained in passage ready for client projects. In conjunction with Crown's capacity to perform large-scale studies screening multiple models in one study, we can perform HuTrial in months, not years.

Our PDX models can be generated from a wide range of cancer types. They are usually implanted as fragments of tumors directly from patients to immunodeficient mice, and they generally retain the histological characteristics of the parental patient tumors. PDX models allow an invaluable assessment of tumor evolution and adaptive response to therapy and have been applied to preclinical drug testing and biomarker identification in a number of cancers, including ovarian, pancreatic, breast, and lung. These models have been shown to be biologically stable and accurately reflect the patient's tumor not only with regard to histopathology, but also in its gene expression, genetic mutations, and therapeutic response. As an integral step in the oncology drug discovery process, cell line derived xenograft (CDX) models provide key decision-making information to allow an agent to move forward. Crown Bioscience has established multiple in vivo assay systems to evaluate novel anti-cancer compounds. Each assay is designed to understand specific aspects of each drug property and its mechanism of action. By using our comprehensive capability, our customers can advance development programs in a timely and cost-effective manner.

There are a total of around 2,000 cell lines available for studies; many of those have publically available profiling data. Crown Bioscience has recently launched the Phase II of Xenobase, a database that combines the publically available profiling data of more than 1,000 cell lines, with our proprietary in vivo pharmacology data. This allows users to make an informed decision by searching for gene mutation, amplification, and expression, as well as tumor growth in vivo and response to Standard of Care (SOC) treatments.

"Our comprehensive drug discovery services and unique portfolio of models for both oncology and metabolic diseases enable our customers to significantly accelerate and improve the quality of their decision-making process about which candidates to move into the clinic. As a preclinical CRO, we provide a unique range of models and services to help our clients accelerate their research and drug development efforts."

Q: What are some of the biggest challenges facing cancer research and the transition of new drugs from preclinical research to clinical trials?

A: The ability to maintain and study immortalised cell lines in an *in vivo* environment has proved to be a valuable tool in cancer research for several decades. These allow key decision-making information and a biologically relevant platform to study disease progression, develop novel therapies to improve treatment options, and allow an agent to move forward from preclinical trials. However, cancer cell lines have usually adapted to grow in culture. The lack of tissue architecture and heterogeneous population of cell types often abolishes cell-cell interaction, secretion, and other functions that depend on tissue context, and, therefore, cannot create an environment well-aligned with that of the patient's tumor. Cells in culture are prone to genotypic and phenotypic drifting. Thereby cell lines can lose tissue-specific functions and acquire a molecular phenotype quite different from cells *in vivo*.

Another challenge facing cancer drug development is the high failure rate in clinical trials and the associated costs. Attrition rates in oncology are significantly higher than in other therapeutic areas, with only 5% of promising anti-cancer agents being licensed after successful Phase III trials. This is reflective of the lack of predictive power of traditional preclinical modelling in which efficacy at preclinical setting fails to translate into clinical benefit. The majority of failures are linked to efficacy rather than toxicity and, combined with the continually rising costs of clinical trials, have resulted in an oncology drug development process, which is both highly inefficient and enormously costly for pharmaceutical companies. In order to improve the efficiency and cost-effectiveness of developing new therapies, current translational tools need to be enhanced to ensure they are of optimum value for indicating clinical success. Effective preclinical precision profiling screening platforms need to be established, which can validate the profile of a prospective drug candidate before entering clinical trials.

The use of relevant models can bring these high attrition rates down and offer a unique opportunity to study drug mechanisms within a tumor microenvironment relevant to patients.

Q: How is Crown Bioscience working to change the cancer drug development and clinical trial processes?

A: The evolution of clinical trials toward study types that find the correct targeted agent for the correct patient groups is crucial as the oncology drug development process is currently

highly inefficient and needs a rapid overhaul to reduce attrition rates.

The key to improve drug discovery programs is the use of genomically characterized PDX models that are truly reflective of the patient population. This results in a model far more closely aligned with a patient's disease than an immortalized cell line, allowing the assessment of tumor evolution and response to therapy.

Recent years have seen a considerable increase in the popularity of PDX models as a platform for the screening of novel therapeutics for the treatment of cancer. Their use in Phase II-like studies or human surrogate trials has significantly changed the way compounds are evaluated prior to transitioning into the clinical setting. By establishing deep biological insights into the pharmacological mechanisms of a drug and identifying potential biomarkers important to clinical trial design, Crown Bioscience's HuPrime models provide drug developers with a significantly higher level of confidence for decision-making in the drug discovery process.

Q: How are your models uniquely qualified and able to address these challenges?

A: Our service can help pharmaceutical companies prioritize lead compounds, narrow down possible disease indication, and identify biomarkers to stratify patient populations in clinical trials, lowering drug attrition rates, and reducing development cost. Preclinical Phase II-like trials utilize a large cohort of PDX models with each PDX subject reflecting the pathology of its original patient (behaving as a patient avatar), and the cohort of patient avatars representing the diversity of the human patient population. Human surrogate trials can help to screen lead drug candidates, discover or validate predictive biomarkers and genetic signatures, and to position or reposition agents through identification of responder populations.

Crown's HuPrime models, without in vitro manipulation, mirror patients' histopathological and genetic profiles, and have been shown to have potential predictive power in the response from the same patients from whom they were derived. A large cohort of HuPrime can thus represent a wide range of disease diversity of patient populations. HuPrime has been increasingly recognized to be one of the most predictive animal models for evaluating anti-cancer therapies.

Q: What do you see as the trends for preclinical research in the future?

A: There is a growing requirement for more relevant models in the preclinical screening of modern drug candidates. By using models that are far more relevant to the clinical situation, in conjunction with precision molecular profiling and data analysis, it is possible to optimise and accelerate therapeutic compounds into the clinic. There is a great unmet need for improved preclinical models, with functional immunity, to drive forward promising research in immuno-oncology and to enable the successful transition of drugs from the laboratory to the clinic.

Models of murine immunity, including syngeneic and genetically engineered mouse models (GEMMs), can be used to interrogate novel immune treatments through activating the mouse immune system, follow the complete process of cancer progression and assess where stimulating the immune system is most beneficial. Newly developing platforms comprising allografts of spontaneous murine tumors, studied in mice with complete immunocompetency (MuPrime™) combine the improved predictive power of GEMM models with an operational simplicity, consistency, and robust growth for pharmacology research.

The oncology research community today is seeking better ways to offer a wider cross section of patients an improved quality of life and potential cures. There is a strong need to have tools available which can significantly improve the qualification of candidates at a much earlier stage in the drug discovery process. Our HuPrime models, as well as GEMM, MuPrime, and syngeneic models, can contribute by different means to move the most promising compounds to the clinic and reduce drug attrition rates by selecting the best clinical strategy. ◆

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THERAPEUTIC FOCUS

Direct Effects™ Cannabinoid Therapy: Medical Cannabis Without Psychoactive & Systemic Effects

By: Ronald Aung-Din, MD

MEDICAL CANNABIS CONTROVERSY

There is no greater medical therapeutics "double-edged sword" than cannabis. Benefits in treating symptoms of diverse conditions have been known for thousands of years. Its psychoactive effects have caused abuse and labeling as a "gateway drug" for more addictive compounds. No class of compounds has generated more controversy and stigma.

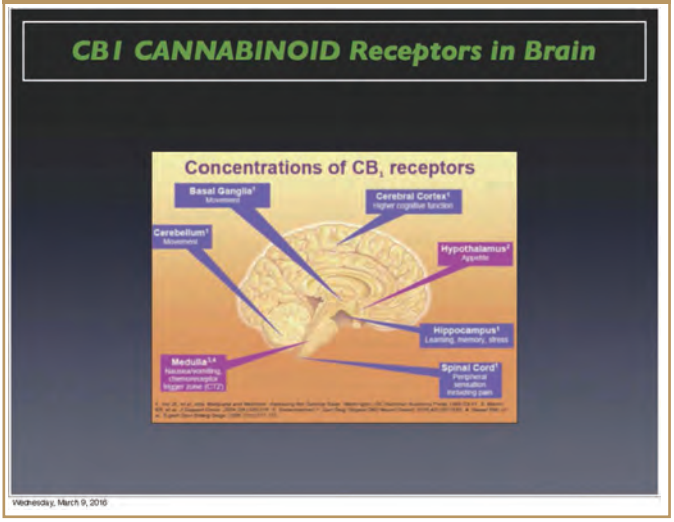
Although defined under federal law as having no medical use, US Patent No. 6630507 was granted in 2003 to the US Department of Health and Human Services for cannabinoids to treat a wide range of diseases. Cannabinoids as Antioxidants and Neuroprotectants claims exclusive rights for treating Alzheimer's, Parkinson's disease, stroke; and states of oxidative stress, such as heart attack, Crohn's disease, diabetes, and arthritis.[1]

Up to the 1900s, medical cannabis was widely marketed and prescribed in the US. In 1890, Eli Lilly and Parke Davis joint-ventured to breed cannabis in Greenfield, IN, producing Cannabis Americana. In 1937, Congress enacted cannabis prohibition.[2]

ENDOCANNABINOID SYSTEM (ECS)

The endocannabinoid system, ECS, consists of cannabinoid receptors located throughout the mammalian nervous system. ECS is involved in a variety of physiological processes, including neurological functions dealing with pain, mood, memory, movement, and sensation. Immune function and cell homeostasis are also maintained by ECS. ECS mediates psychoactive effects of cannabis. Cannabinoids are a diverse class of compounds that include those in cannabis.[3,4]

FIGURE 1



Two primary endocannabinoid receptors have been identified. CB1 receptors are predominantly in the brain and nervous system as well as in peripheral organs and tissues. These are acted on by the endocannabinoid Anandamide. The other main endocannabinoid, 2-Arachidonoylglycerol (2-AG), is active at both the CB1 and CB2 receptors. Its mimetic phytocannabinoid is cannabidiol, CBD; that of Anandamide is

THC, responsible for psychoactive effects. Both 2-AG and CBD are involved in appetite regulation, immune function, and pain management.[5,6]

CANNABINOIDS INFLUENCE NEUROTRANSMISSION & INFLAMMATORY RESPONSE

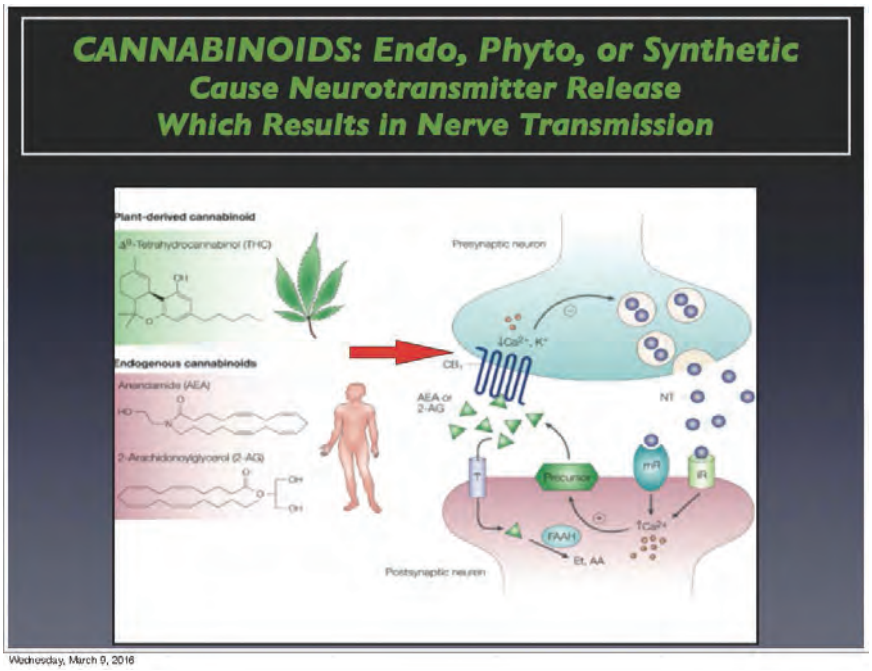
Cannabinoids act on cannabinoid receptors on cells to influence neurotransmitter release. Endocannabinoids are produced naturally in humans and animals, phytocannabinoids in cannabis and some other plants; and synthetic cannabinoids are chemically manufactured. Δ9-tetrahydrocannabinol (THC), is primary psychoactive compound of cannabis. Cannabidiol (CBD), making up to 40% extracts of plant resin, has varied medical benefits. At least 85 different cannabinoids have been isolated from cannabis.

Cannabinoids produce physiological and behavioral effects through specific membrane-bound receptors. CB1 receptors are found in the brain and are responsible for euphoric and anti-convulsive effects of cannabis. CB2 receptors in the peripheral nervous system appear responsible for anti-inflammatory effects, such as pain relief.

CANNABIDIOL (CBD): "MEDICAL COMPONENT" OF CANNABIS & HEMP

Cannabidiol, CBD acts as serotonin (5-HT1A) receptor agonist, which may explain its antidepressant, anxiolytic, and neuro-protective effects.[7,8] CBD

FIGURE 2



modulates opioid receptors involved with pain perception.[9] CBD is not psychoactive and relieves convulsion (seizures), inflammation, anxiety, and nausea. It has been found to prevent short-term memory loss from THC. Antipsychotic effects of cannabidiol represents potential treatment of schizophrenia.10-12 CBD has a greater affinity for CB2 than CB1 receptors.

CBD is considered to have a wide scope of medical applications. An oral CBD formulation received orphan drug status in the US for Dravet syndrome, an intractable seizure disorder, Severe Myoclonic Epilepsy of Infancy (SMEI). Nabiximols (Sativex) is an aerosolized oral mist of CBD and THC approved in Canada for multiple sclerosis pain.[13,14]

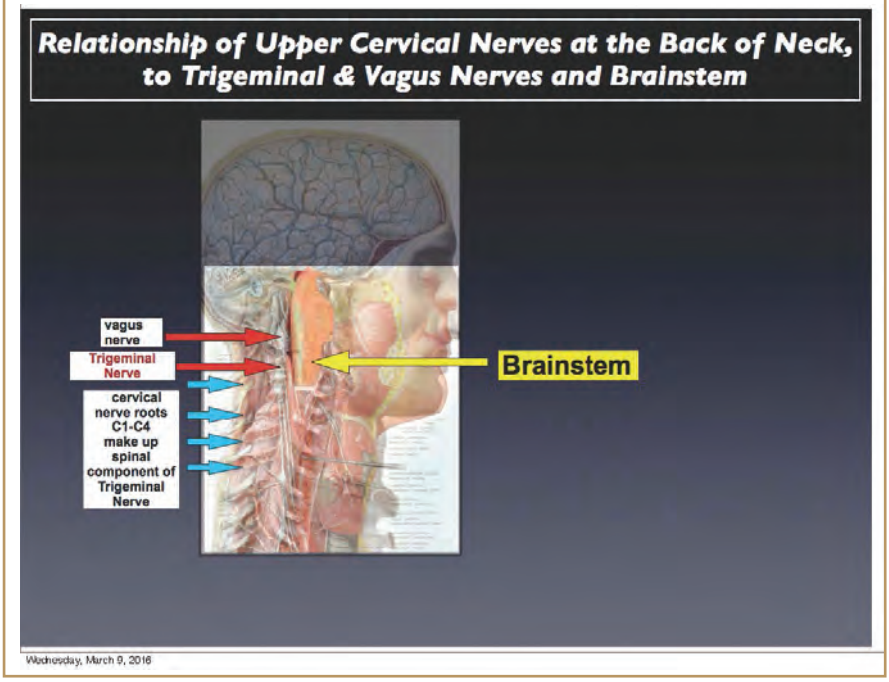
CBD has been found safe and well-tolerated as treatment for schizophrenia. A double-blind trial compared cannabidiol to atypical antipsychotic amisulpride in acute paranoid schizophrenia. Both treatments showed significant decrease in psychotic symptoms, but cannabidiol had fewer side effects. Studies also show cannabidiol decreased symptoms of social anxiety and isolation.[15,16] Cannabidiol has demonstrated antidepressant-like effects in animal models of depression.

POTENTIAL OF DIRECT EFFECTS™ TOPICAL CANNABINOID THERAPY

A major shortcoming in cannabinoid therapy is its potential for undesirable side effects. Of particular concern is in children with intractable epilepsy, exposing developing brains to unknown long-term effects of systemic cannabinoids. Direct Effects Topical Drug Delivery provides a potential solution.[17-19]

In view of the beneficial effects of CBD in various neuropathic and psychiatric conditions, studies were performed with Direct Effects topical delivery of CBD applied as cream to the back of the neck (BON) and other areas of the spine and peripheral nerves, as

FIGURE 3



appropriate. Intent is modulating neural afferents to affect efferents as relief of pathologic symptoms. BON is unique considering the magnitude of available afferent input available through skin-free nerve-endings.

Direct Effects is a means to deliver CNS-active drugs, including cannabinoids, through activating neuro-chemical receptors existing on free nerve-endings. There exist hundreds of thousands to millions of free nerve-endings below the skin surface (stratum corneum) at the upper posterior cervical region, BON. Cervical nerve roots, C1-C4, and occasionally C5 provide direct neural connections to afferent components of the trigeminal, vagal, and cervical sympathetic nerve systems inputting CNS. No other location has such a magnitude of afferent neural input accessible through skin nerve-endings.

Modulated CNS efferents responding to afferent activation results in improvement of symptoms of brain and spinal cord dysfunction. In using direct nerve pathways without restrictions of blood flow and the blood-brain-barrier, therapeutic onset is greatly reduced, and systemic side effects are avoided.

Direct Effects therapy has rapid therapeutic onset of action of less than 10 to 15 minutes, and maximal benefit within 30 minutes. Therapeutic effect is 4 to 12 hours or more, depending on condition and severity.

Direct Effects drug delivery has been used with success with sumatriptan in migraines, apomorphine in Parkinson's disease and related movement disorders, and tizanidine in muscle spasm and tension headache. US and international patents have been granted in these areas. In view of superiority of topical delivery as compared to systemic use as oral tablet, injection, nasal spray, or transdermal patch, it was believed cannabinoids could be similarly applied as a cream to treat symptoms of neuropathic conditions. This was of particular interest in view of known systemic side effects of inhaled and ingested cannabinoids.

FIGURE 4

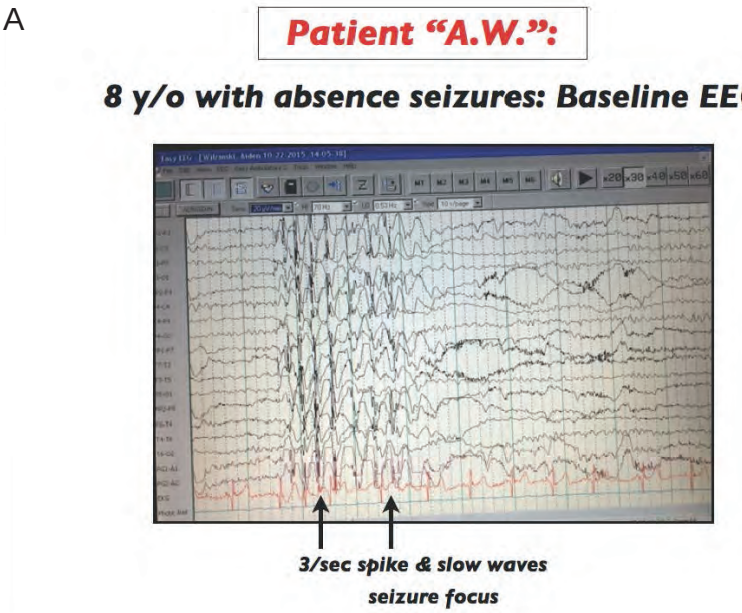
CLINICAL RESULTS WITH TOPICAL CBD

In a study of 88 patients, topical CBD was found effective in treating the symptoms of the following conditions:

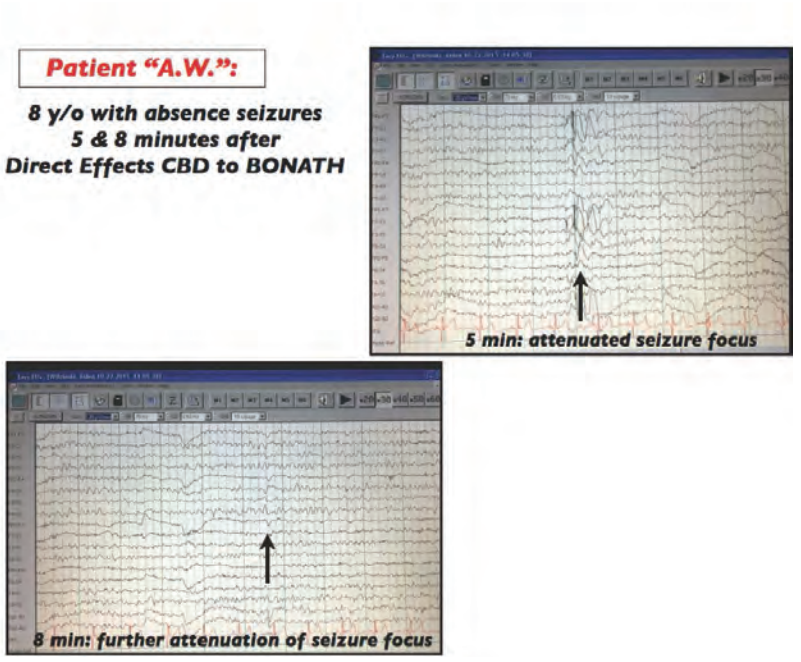
- Seizures
- Encephalopathy, including lethargy, inattention, and cognition
- Spasticity
- Weakness
- Pain, including radiculopathy and shingles
- Numbness
- Anxiety and other mood disorders, including PTSD
- Hypertension
- Parkinson's disease
- Insomnia
- Bell's palsy and facial nerve dysfunction
- Trigeminal Neuralgia
- Hemi-facial spasm
- Autism/Asperger's
- Attention Deficit Disorder & Hyperactivity
- Social Isolation
- Occipital Neuralgia
- TMJ dysfunction-related symptoms
- Cognitive problems, including memory disturbance
- Peripheral Neuropathy
- Essential Tremor

FIGURE 5

A



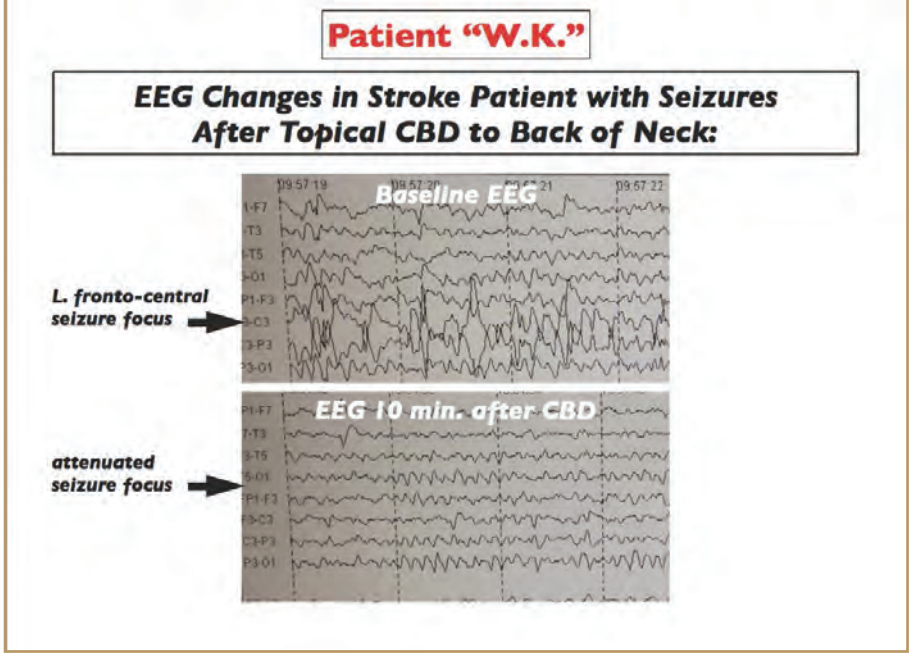
B



Breakdown of major clinical categories:

- 34 subjects with seizures, encephalopathy, and spasticity responded to topical CBD therapy at BON
- 13 subjects with headaches and neck pain benefitted from topical CBD application to BON
- 16 subjects with back/spin and extremity pain, fibromyalgia achieved relief with topical CBD applied at BON and at other appropriate spinal and extremity/peripheral locations
- 6 subjects with Parkinson's, tremors, movement disorders responded to topical CBD treatment at the BON

FIGURE 6



- Dosing frequency ranged from once daily to 3x/day depending on chronicity and severity of condition; and individual response to topical CBD therapy (each 1-g dose contained 1.5 to 3% CBD)

- Duration of treatment with topical CBD ranged from several days to as needed/prn for relief of episodically symptomatic disease states; to months of continued daily therapy for chronic conditions, such as epilepsy, Parkinson's/movement disorders, and spasticity with permanent symptoms or impairments

- The longest continuous use period in the aforementioned patients was 6 months of 2x/day for a 7-year-old male with absence seizures; however, the longest period of continued use for any patient with topical CBD is18 months for intractable epilepsy (refer to Figures 5a and 5b showing attenuation of absence seizure focus, 3/second spike and slow wave complexes, with topical CBD therapy at BON)

- No systemic side-effects were observed or reported in any subject exposed to topical CBD. Several patients (less than 10%) reported itching or slight rash at CBD cream application site. The formulation was changed in these cases.

- In some patients on long-term medications, some previous medications were lowered or discontinued as a result of clinical improvement from topical CBD

CONCLUSION

Topical CBD is beneficial in treating symptoms of a number of neuropathic and psychiatric conditions. Individual clinical response varied depending on condition treated and on severity and longevity of symptoms. Topical CBD therapy was overall well tolerated.

In a few instances, topical CBD treatments rendered subjects free of symptoms that had been present for some time. This suggests "neural re-programing" and re-establishment of homeostasis. This possibility of disease modification and pathologic process reversal deserves further investigation. It places cannabinoids in a unique category of therapeutic compounds. Studies in rat models of MS have suggested such phenomena with re-myelination of de-myelinated areas with CBD therapy.

Some conditions were more responsive to topical cannabinoid therapy than others. Seizure disorders and epilepsy responded most robustly to topical CBD application at BON. Complete seizure freedom was achieved in a number of patients with previous intractable epilepsy on multiple drug regimen. ◆

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Ronald Aung-Din, MD, practices General Neurology and Neuropsychiatry in Sarasota, FL. Through affiliation with Lovelace Research Institute, Albuquerque, NM, he has functioned as Principal Neurology Investigator in over 60 clinical trials, helping bring to market drugs in Epilepsy, Multiple Sclerosis, Neuropathic Pain, and Parkinson's Disease. In May 2009, Dr. Aung-Din founded AfGin Pharma, LLC, a research and development biopharmaceutical company dedicated to Direct Effects Topical Neuro-Affective Therapy, a novel non-systemic delivery of neuro-active compounds he discovered useful in treating neurological and neuropsychiatric conditions. The therapy is unique in that rapid (within 10-30 mins) therapeutic results are achieved without usual systemic side effects and drug interactions. To date, 7 patents relating to the technology have been granted by USPTO and the EU and Australian patent offices, with others filed and pending.

ANTIGEN-SCREENING SYSTEM

Perfecting the Promise of T Cell Therapies for Infectious Disease & Cancer

By: Jessica B. Flechtner, PhD

THE EVOLUTION OF IMMUNOTHERAPIES

The human body is armed with an efficient and elegant immune system that fights pathogens and tumor cells using T cells and antibodies made by B cells. Throughout the past century, incredible advances have transformed the way we think about harnessing the immune system's potential to fight the most dreaded diseases.

Despite multiple immune mechanisms that can be employed to fight diseases, the majority of vaccines approved to date are thought to work principally through antibody responses created by B cells only. Experts agree that the future of successful vaccine development in infectious disease and in the fight against cancer is to go beyond the B cell – and engage the T cell arm of the immune system to more comprehensively employ the natural armament.

Attempts to date to create immunotherapies based on directing T cell responses have largely focused on engaging T cells to respond to known targets of B cell response – and have often failed. These failures suggest that the key to harnessing the entire adaptive immune system to fight disease is to identify the right T cell targets that will induce a protective response.

This leaves vaccines and immunotherapies at a critical crossroads – with a new technology poised to help us see what was previously hidden and fully deliver on their promise.

THE T CELL CONUNDRUM

Unlike antibody targets, which are typically surface-expressed or secreted proteins, T cell targets can be derived from ANY protein in a pathogen or cancer, increasing the potential target pool by up to a thousand-fold. Human genetic diversity further increases the complexity. Here's why. One of the first lines of defense in our body is white blood cells called antigen-presenting cells (APCs). The job of an APC is to sample its environment. For example, when a virus enters the body, a patrolling APC will "eat" it and break down all of the viral proteins into small pieces. The APC will then present some of the small pieces of the viral proteins on its surface to nearby T cells that are trained to differentiate "good" from "bad" pieces. Importantly, each person's APCs have unique ways to chop and present protein pieces to their own T cells. If the T cells recognize the piece as "bad" then it will multiply, search for, and kill all cells harboring the virus.

This means that in every person, any piece of that virus has the potential to be recognized as foreign and constitute an antigen, but not all are. As a result, the sheer volume of potential antigens – a.k.a. T cell targets – in a complex pathogen or cancer and the differences in how they may be presented by each person's APCs makes reliable predictions of which antigens to include in a vaccine virtually impossible. In addition, just because a T cell can "see" the target, it does not necessarily mean that a response to that antigen is protective. In fact, associations of T cell responses with clinical outcomes are required to prioritize T cell antigens effectively. The development of a tool that is able to cut through the complexity

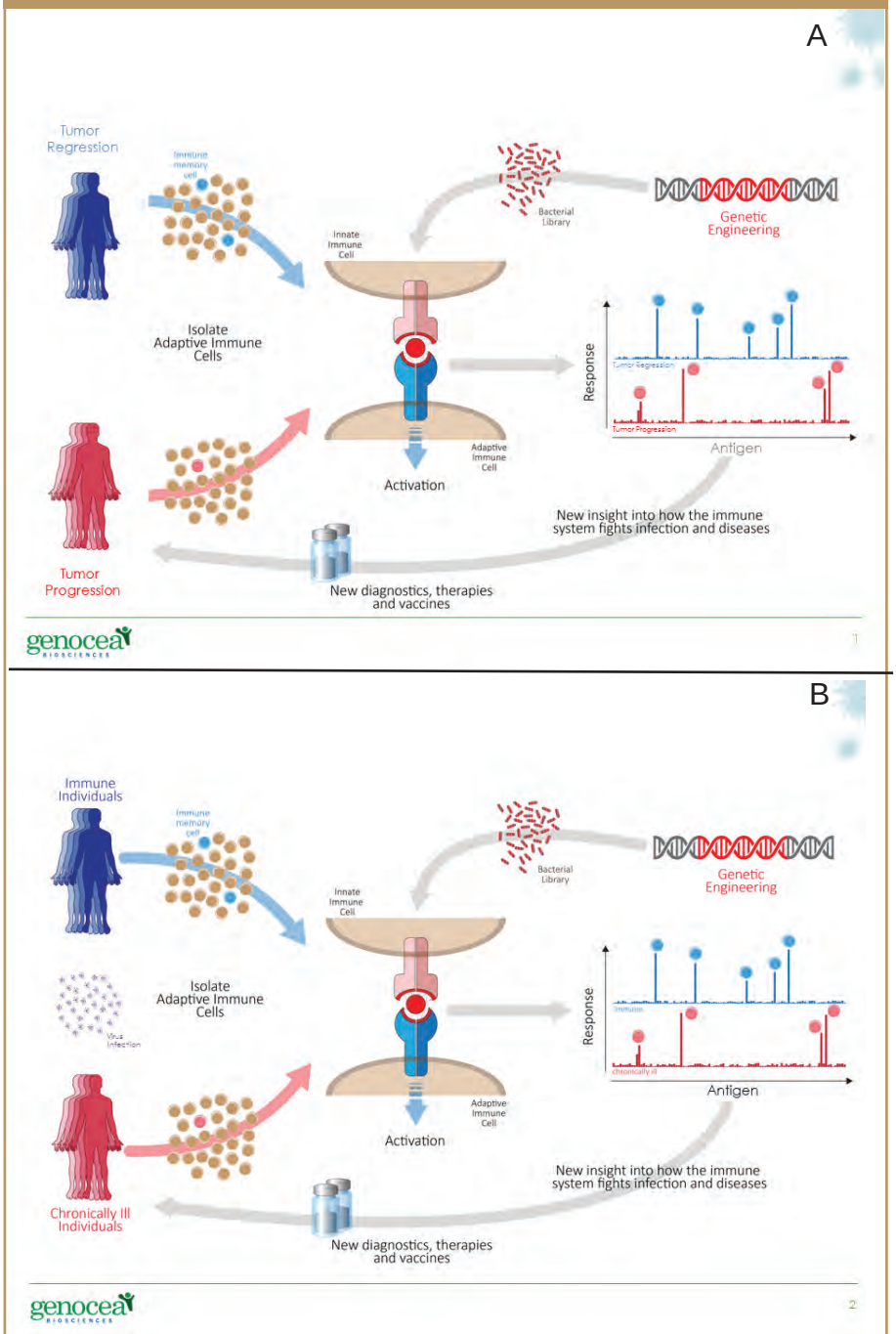
of human diversity and the magnitude of potential targets, in order to identify the right T cell antigens which drive a protective immune response, could unlock a wealth of treatments to better fight diseases for which no good solutions exist.

BETTER PROFILING, BETTER TARGETING

Genocea Biosciences is working to remove these barriers by finding clinically relevant antigens (those that elicit protective T cell responses) in diverse human subjects to guide the development of new immunotherapies. At the core of the company's mission to commercialize key breakthroughs in vaccine and immunotherapy discovery and development is Genocea's proprietary technology, ATLAS™, which solves many of the challenges associated with finding the right T cell targets. Using ATLAS, Genocea is cultivating a pipeline of immuno-oncology and infectious disease-related clinical and preclinical candidates.

ATLAS, a first of its kind, proprietary rapid antigen-screening system identifies, via a cellular assay, what the T cells of people who naturally protect themselves against disease do differently than the T cells of those who don't. In order to detect the most important T cell responses, ATLAS is unbiased: rather than predicting which antigens are meaningful, it instead takes a panoramic snapshot of actual human T cell responses to any possible T cell target in a pathogen or cancer. By associating these individual T cell response signatures with differential clinical

FIGURE 1A&B



The ATLAS process used to identify T cell targets in immuno-oncology and infectious diseases.

outcomes across large cohorts of patients, ATLAS can select the most clinically relevant T cell targets for vaccine and immunotherapy development.

As a result, ATLAS winnows what can be as many as several thousand candidate antigens down to a small set of antigens that correlate with natural immunity. A subset is selected for *in vivo* testing with the goal of identifying antigens for formulation and development into vaccine candidates that will stimulate protective or therapeutic immunity across diverse populations.

Because antigens are identified by

ATLAS using actual human immune responses to all potential targets, by the time these candidates reach clinical trials, there may be a greater likelihood of success in clinical development.

INNOVATION IN INFECTIOUS DISEASE

Genocea's lead clinical candidate is GEN-003, a first-in-class immunotherapy to treat genital herpes by inducing both T cell and B cell (antibody) immune responses. GEN-003 has demonstrated first-in-class results to date by showing statistically significant reductions in clinical signs of genital herpes and viral shedding. The antigens included in the GEN-003 vaccine were discovered using ATLAS.[1]

Genital herpes is a serious and incurable sexually transmitted disease that affects more than 500 million people worldwide,[2] including one out of six people between the ages of 14 to 49 in the United States.[3] The disease can cause painful symptoms that include "outbreaks" in the form of blisters, usually on or around the genitals and anus. People with genital herpes can still be highly infectious even if they are not experiencing noticeable symptoms, and more than 80% of infected individuals ages 14 to 49 in the United States go undiagnosed.[4] While available antiviral treatments can help prevent and shorten genital herpes outbreaks,[5] there is a significant unmet need for therapeutic approaches that better control symptoms and viral shedding (the active viral state when transmission risk is greatest).

In October 2015, Genocea reported positive results from its Phase 2 trial of GEN-003 6 months post dosing. Vaccination with GEN-003 resulted in a statistically significant 58% reduction from baseline in the viral shedding rate, the primary endpoint of the study. The proportion of patients receiving GEN-003 who were lesion-free at 6 months after dosing ranged from approximately 30% to 50%, similar to results reported in clinical trials with chronic administration of oral antiviral therapies. The study also found that GEN-003 was safe and well tolerated by patients, with no serious adverse events related to the vaccine.

GEN-003 most recently demonstrated sustained and statistically significant reductions compared to baseline in the rate of viral shedding 12 months after dosing, with sustained efficacy at multiple dose levels across secondary endpoints measuring the impact on clinical disease. The company has advanced the two most promising doses, of 60 µg per protein combined with either 50 or 75 µg of Matrix-M2™ adjuvant, from this Phase 2 dose optimization study into an ongoing Phase 3 efficacy trial. Later this year, the company will report virologic and clinical efficacy data using potential Phase 3 endpoints from the Phase 2B trial, confirming the activity of GEN-003 manufactured at larger scale. Genocea will also commence a Phase 2B antiviral combination study in the second half of 2016.

GEN-003 has the potential to become a cornerstone treatment for genital herpes patients. A single course of GEN-003 may offer genital herpes patients efficacy similar to a full year of daily administration of oral antivirals – but with vastly improved convenience. Furthermore, in contrast to the dominant treatment paradigm of episodic antiviral treatment, GEN-003's ability to reduce viral shedding could decrease the frequency of genital lesion outbreaks and may potentially lower the risk of disease transmission for these patients.

TABLE 1

	60 µg per protein/50 µg of Matrix-M2			60 µg per protein/75 µg of Matrix-M2		
Endpoint	Post dose 3	6 months	12 months	Post dose 3	6 months	12 months
Viral shedding rate reduction*	41% (p < 0.0001)	46% (p < 0.0001)	66% (p < 0.0001)	55% (p < 0.0001)	58% (p < 0.0001)	54% (p < 0.0001)
% patients lesion free	68%	36%	30%	68%	30%	21%
Genital lesion rate reduction*	69% (p < 0.0001)	50% (p < 0.0001)	65% (p < 0.0001)	60% (p < 0.0001)	43% (p < 0.0001)	47% (p < 0.0001)

*Rate reduction vs. pre-dosing baseline levels. Poisson mixed effect model analysis.

Summary of data from the Phase 2 dose optimization trial.

ATLAS & IMMUNO-ONCOLOGY: CHARTING A CLEARER PATH FORWARD

ATLAS' capabilities are currently also being leveraged to help take the guesswork out of cancer vaccine T cell target discovery and better identify patients most likely to respond to immuno-oncology therapies through partnerships with the Dana-Farber Cancer Institute and Memorial Sloan Kettering Cancer Center.

The Dana-Farber Cancer Institute collaboration sees Genocea using ATLAS

to study tumor-associated antigens in melanoma patients treated with checkpoint inhibitors. By profiling their T cell responses to different cancer antigens, Genocea may be able to understand their clinical relevance. A retrospective analysis of the T cell responses from checkpoint inhibitor-treated patients against known tumor-associated antigens revealed that ATLAS had successfully identified the cancer antigens to which T cells naturally had become activated. This research also demonstrated a pattern indicating that different characteristics of T cell responses emerge in patients who responded to checkpoint inhibitor therapy versus those who did not.

In the Memorial Sloan Kettering Cancer Center collaboration, Genocea is using ATLAS to screen the T cell responses of melanoma and non-small cell lung cancer patients treated with checkpoint inhibitors against their own, patient-specific tumor neoantigens. This research is aimed at identifying signatures of protective T cell responses with the goal of potentially discovering new cancer vaccine T cell antigens.

The research conducted by Genocea alongside these leading academic centers demonstrates ATLAS' flexibility to help optimize the development of both universal and personalized cancer vaccines. When applied across large diverse populations against common tumor-associated antigens, ATLAS may discover better targets to include in cancer vaccines, which could potentially help them work more broadly across different patient populations. When applied to an individual's response to their own cancer neoantigens, ATLAS may enable better personalized cancer vaccines, either as standalone therapies or in combination with other immunotherapies, such as checkpoint inhibitors.

With additional data from its ongoing immuno-oncology collaborations expected in 2016, Genocea anticipates initiating trials for a personalized cancer vaccine candidate in 2017.

CONCLUSION

Based on the information and insights gleaned from ATLAS, Genocea has been able to successfully define targets of human T cell responses that become central to novel vaccines and immunotherapies, and demonstrate success in a clinical setting. Effective therapies which direct T cells against cancer and infectious diseases could revolutionize healthcare and improve outcomes for patients affected by these illnesses. The right T cell targets, discovered with ATLAS, are the key to unlocking the full promise of T cell therapies, finding solutions for the most challenging and hardest to treat diseases. ◆

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BIOGRAPHY

Dr. Jessica Baker Flechtner joined Genocea in 2007, soon after the company was founded, and currently serves as the Chief Scientific Officer. Dr. Flechtner is a pioneer in the development of novel vaccines directed toward T cell immunity and has more than 18 years of experience in immunology, infectious disease, cancer, and vaccine development. She leads Genocea's efforts to develop T cell-directed vaccines and immunotherapies against infectious diseases and other indications. Prior to joining Genocea, Dr. Flechtner developed vaccines and immunotherapies for cancer, infectious disease, autoimmunity, and allergy in several companies, including Mojave Therapeutics and Antigenics Inc. (now Agenus). She is an inventor on seven pending and three issued patents and has multiple peer-reviewed scientific publications. Dr. Flechtner performed her post-doctoral work at the Dana-Farber Cancer Institute and Harvard Medical School. She earned her PhD in Cellular Immunology and her BS in Animal Science from Cornell University, and is a member of the American Association of Immunologists and American Society for Microbiology.

RIGHTS MANAGEMENT PROTECTION

You Have the Right to Remain Protected

By: Tom Johnson, Senior Director, Life Science Solutions, Exostar

INTRODUCTION

Pharmaceutical companies are like any for-profit business. Although the products they develop, produce, and sell may improve or save lives, they are not necessarily philanthropists. Their ultimate objective is to generate revenue and maximize profit. In so doing, they not only satisfy investors and shareholders, they also help drive the economy by directly and indirectly creating jobs. They also reinvest to support the research needed to identify the next generation of drugs and therapies.

Achieving the objective is becoming increasingly difficult. Clinical trials and other regulatory requirements and constraints extend the research and development (R&D) process to as much as 10 years, with a cost of between $1.5 and $3 billion to bring a product to market. This timeline shrinks the window between product introduction and patent expiry, placing enormous pressure on the commercial side of the business to recover the R&D investment. The commercial side faces additional costs associated with complying with sales- and marketing-based disclosure requirements, along with public pressure to keep drug prices affordable for all.

Pharmaceutical companies have responded by looking for ways to reduce their R&D and commercial costs while at the same time getting new products to market quicker so they open a wider window to patent expiry. As a result, the business model continues to move in the direction of partners and automation. A global partner network opens the door to accelerating schedules and minimizing expenditures by leveraging niche expertise and engaging resources when and where they are most needed. Automation eliminates the manual, paper-based activities that can introduce errors and performance drag. Enhancing the collaborative experience is critical to the successful operation of a partner network that can include contract research organizations, academia, investigators, marketing agencies, and others.

The partner-centric business model offers the time and cost benefits pharmaceutical companies seek so they can make a reasonable profit while selling drugs at a fair price. However, it also introduces significant risks as sensitive information and intellectual property are shared beyond enterprise boundaries. If documents and data fall into the wrong hands, the impacts can be seismic – just ask Pfizer and Eli Lilly, both of whom have suffered the consequences recently.

SECURITY MUST BE A PRIORITY

Implementing and enforcing strong security policies is a challenge even within a pharmaceutical company's enterprise. IT has a fighting chance though because the problem is bounded, with users, devices, and applications generally well-known. The introduction of a partner network with external organizations, individuals, systems, and devices raises the stakes to new heights, making the deployment of cloud-based identity and access management and business-to-business collaboration solutions an imperative.

A cloud-based identity and access management solution is a foundational security component. The solution provider can work with pharmaceutical companies and their partners to conduct identity-proofing activities for all individuals and to ensure all proofed individuals receive valid credentials. These

credentials can be issued by the solution provider or they can be native credentials issued by the organization to which the individual belongs. The solution controls access to applications by authenticating the presented credentials (thereby verifying the individual's identity) and granting access based on permissions assigned to an individual by application owners. Individuals enjoy a seamless, single sign-on user experience, while application owners maintain access control across the network of partners.

A cloud-based business-to-business collaboration solution extends the reach of a more traditional enterprise collaboration application to support secure collaboration amongst partners. To do so, the solution should be architected for multi-tenancy (to segment information and limit document visibility to those who qualify to participate in a collaborative effort). The solution also should protect data at-rest (through database encryption) and data in-transit between partners (through end-to-end encryption). Finally, the solution should work in tandem with an identity and access management solution. With this pairing, the business-to-business collaboration solution can support multi-tiered security tied to the strength of credentials issued to individuals. At higher tiers, the collaborative functionality becomes even more limited to better protect information exchange. For example, WebEx attendance can be limited to only those individuals who possess a certain strength of credential and have been identified as part of the current collaborative activity.

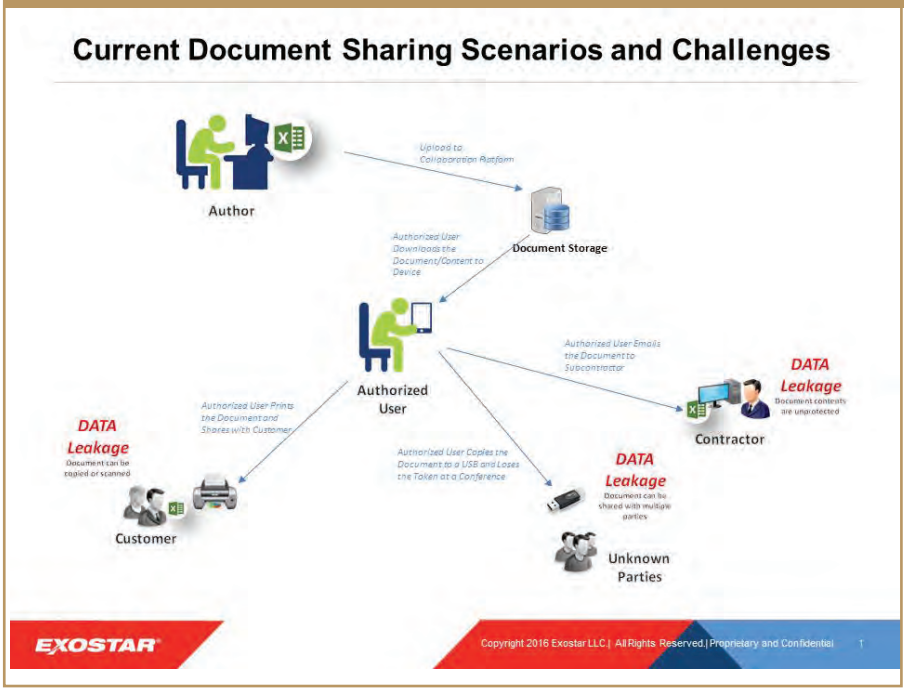
While identity and access management and business-to-business collaboration solutions go a long way toward providing the security pharmaceutical companies need to adopt an external partner network business model for drug development and delivery, they don't completely eliminate the possibility that intellectual property will be compromised. Consider the following scenarios, where an authorized individual accesses and downloads a document in a clinical trial master file:

1. The individual prints out the document, but leaves it unattended in a public place. The document can be scanned, copied, or stolen.

2. The individual saves the document locally, and then forwards it via email to a group of colleagues. Unfortunately, some of these colleagues are not part of this particular phase of the trial and thus should not have access to the information.

3. The individual copies the document to a USB to review at a conference. The individual misplaces the USB or leaves it unattended, and whoever finds it now has access to the document.

FIGURE 1

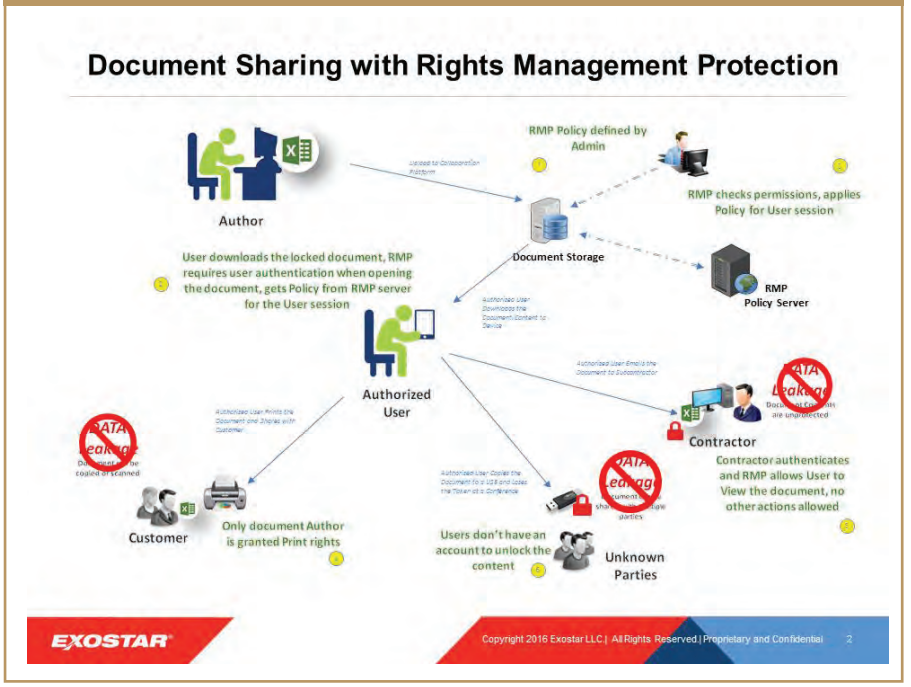


In each case, the identity and access management and business-to-business collaboration solutions did their jobs from a security perspective. The problem arose when the legitimate individual downloaded the document and took a subsequent action that produced a data leakage. These scenarios underscore the need to extend security to the document level, where a finer-grained layer of protection can be applied.

WELCOME TO THE WORLD OF RIGHTS MANAGEMENT PROTECTION

Early attempts to secure the integrity of documents revolved around the use of PDFs. These view-only versions may have

FIGURE 2



prevented a document from being modified, but not from being printed, copied, or shared. As a result, PDFs added little in terms of security, and made collaboration a cumbersome, unsatisfying experience.

Rights management protection addresses the security and convenience shortcomings of PDFs. The key concept behind rights management protection is the assignment of policies at the document level. Policies can include the ability to view, edit, print, or share the document. These policies can be applied to the document universally so all individuals wishing to access the document are treated consistently. Policies also can vary and be tied to an individual's role or permissions.

For example, policies can differ for individuals who work for one partner versus another, based on the responsibilities of each partner organization in a clinical trial. Policies can be based on the time of day, day of the week, duration, physical location, IP address range, or other criteria. These policies follow the document no matter where it travels, and the document owner or administrator maintains full control, with the power to change policies at any time with immediate enforcement.

Rights management protection offers flexible and powerful security, picking up where identity and access management and business-to-business collaboration solutions leave off. With rights management protection, individuals can work in a document's native application mode, such as Microsoft Word or PowerPoint, which enhances the user experience and streamlines collaboration with partners. In addition, when a new version of a document is created, access to the prior version can be turned off, promoting version control, mitigating confusion and risk, and supporting auditing and compliance initiatives.

PICKING THE RIGHT TYPE OF RIGHTS MANAGEMENT PROTECTION SOLUTION

While the concept of rights management protection is straightforward, how such a capability is implemented makes a huge difference for pharmaceutical companies. There are at least three deployment alternatives.

Enterprise-centric rights management protection applications are just that: limited to the boundaries of the enterprise. They can be paired with enterprise collaboration solutions and basic identity and access management solutions to provide outstanding security within the confines of the enterprise. That said, there is no certainty the protections assigned within the enterprise IT domain will be applied and supported when a document makes its way to an individual's device outside of that domain. The partner network business model of today's pharmaceutical industry requires an inter-enterprise purview, not one that is intra-enterprise.

Stand-alone rights management protection applications can be deployed in multi-enterprise environments to deliver the requisite security for documents to be shared between pharmaceutical companies and their partners. This architecture leads to significant overhead, as document owners and administrators must access a separate system each time a policy is to be changed for an existing document or created for a new document. Depending on precisely how the stand-alone application fits within the overarching infrastructure, individuals may need additional identities and credentials to access the application. The

consequences are loss of productivity and the introduction of risk with more security information for individuals to manage.

The ideal approach is an embedded rights management protection application, where the application is integrated with the business-to-business collaboration solution. An embedded rights management protection application means its document-level policies can be directly correlated with the roles and permissions and at-rest/in-transit encryption provided by the cloud-based identity and access management and business-to-business collaboration solutions. Roles, permissions, and policies that are already set get extended, with no additional effort required. As an individual's roles and permissions change over time, so do the policies assigned to that individual for document access.

As a consequence, the right policies get applied at the right time across the partner network – automatically. Rights management protection becomes truly dynamic, as opposed to a series of static snapshots that change over time. By integrating with the collaborative process where collaborative spaces and workgroups are defined, rights management protection becomes part of the workflow between pharmaceutical companies and their partners. The result is a consistent, easy-to-understand, more streamlined architecture. It is also more secure, because no additional identities or credentials need be issued. The approach also supports forthcoming industry direction toward multi-factor authentication and step-up access as an individual's role or the level of information sensitivity changes.

EMBEDDED RIGHTS MANAGEMENT PROTECTION USE CASES

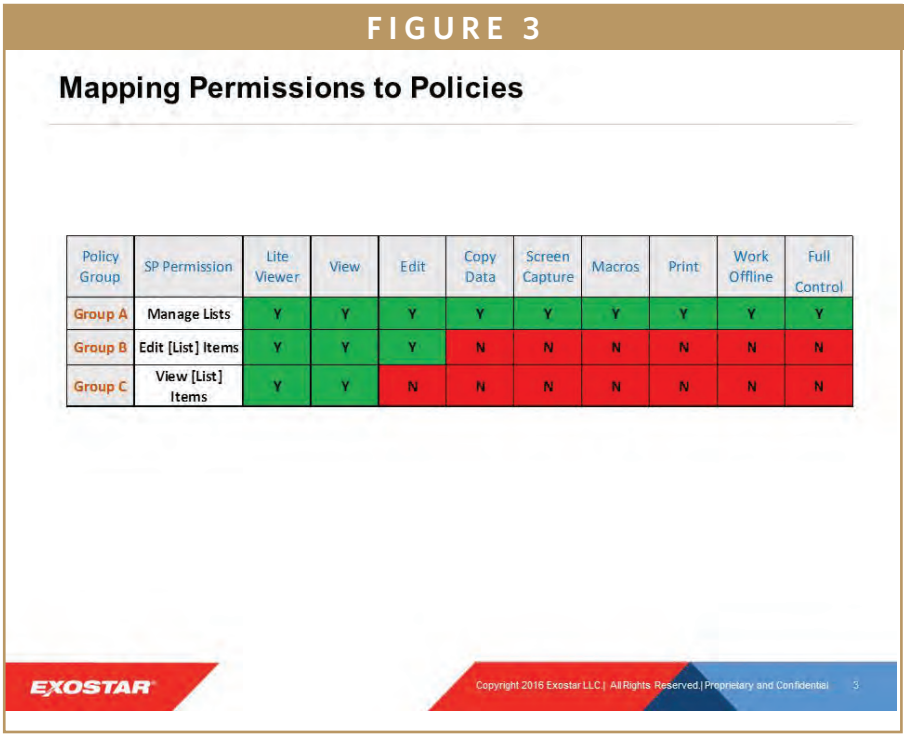
Rights management protection can play a vital role throughout the drug development and delivery process. Pharmaceutical companies can and are taking advantage of its benefits on the clinical R&D and commercial sides of the business.

One of the biggest challenges to clinical R&D is completing Phase III trials on time. Delays can cost upward of $10 million, and often are driven by the need to exchange sensitive content in a highly secure manner. In response to this requirement and concern, pharmaceutical companies and their partners often rely on paper-based document sharing or the creation of siloed collaboration solutions. This methodology introduces drag and inconvenience, and encourages workarounds, which in turn reduce the level of security rather than increase it.

One leading pharmaceutical company estimates that more than one-third of its employees who work with external partners are engaged in the exchange of sensitive content. It has decided to apply rights management protection to its clinical R&D activities by choosing to extend its cloud-based business-to-business collaboration solution with embedded rights management protection. In so doing, the pharmaceutical company is marrying the policies of rights management protection with the permissions assigned to collaboration solution users. Permissions and access are enforced by the cloud-based identity and access management solution to which the collaboration solution is connected.

With this architecture in place, the pharmaceutical company can establish higher-order security for sensitive content. It can require multi-factor authentication for access to sensitive collaboration solution sites, and assign stronger policies for viewing, printing, and sharing documents containing sensitive

FIGURE 3



content. Clinical trials participants get seamless access, can work productively in the document's native environment, and sensitive content can be controlled throughout the trial, including turning off access entirely to certain parties once the phase has been completed.

For commercial endeavors, rights management protection can reduce the time between product approval and product market introduction. Pharmaceutical companies face strict guidelines on how they can promote their products. Everything from the external packaging, package insert, collateral materials, and advertising must be consistent and approved by the Office of Prescription Drug Promotion (OPDP). Before content even gets to the OPDP, it must be created, reviewed, and edited by constituencies within the pharmaceutical company (including marketing, medical affairs, and regulatory teams) and third-parties (including branding agencies and outside legal counsel).

While this content may not expose intellectual property, it certainly must be protected from a competitive advantage standpoint. The traditional approach to securing this content as it makes its way from asset creation and management to review and approval and ultimately compliance confirmation has been similar to the clinical R&D use case – reliance on paper-based exchange or siloed collaboration solutions. More recently, pharmaceutical companies have begun to embrace rights management protection, but have opted for enterprise or stand-alone applications, which don't unleash the full power of the technology. By turning to the embedded rights management protection application, pharmaceutical companies can more quickly and more securely navigate the commercial process for product introduction and subsequent marketing campaigns.

RMP = ROI

On the surface, rights management protection may look like another expense and another system to maintain. While that may be true, it is a critical security component that delivers rapid and significant return on investment. A single security breach during the drug development and delivery process can lay waste to hundreds of millions of dollars of R&D cost and years of effort. The inefficiencies of collaborating with external partners in the absence of rights management protection can cause unnecessary loss of productivity and needlessly drive up capital and operating expenditures.

Cloud-based business-to-business collaboration solutions with embedded rights management protection applications and an integration to a cloud-based identity and access management solution extend the blanket of security to individual documents by bringing permissions and policies together. Pharmaceutical companies can confidently engage with their external partner networks because they have complete control over who can access which collaboration sites and their associated documents at which times and places, and with what privileges. Sensitive information and intellectual property are secured, yet individuals benefit from a seamless, single sign-on user experience and the ability to work within a document's native environment. By exercising their right to remain protected at all times, pharmaceutical companies can achieve their objective of getting new drugs and therapies to market more quickly and cost-effectively – to the benefit of us all. ◆

BIOGRAPHY

Tom Johnson has over 25 years of experience guiding process improvement, managing technology deployment, and directing program teams in the Life Science, Healthcare, and Aerospace and Defense industries. He currently serves as Senior Director of Life Science Solutions at Exostar. In this role, Mr. Johnson leads the company's Life Science secure business collaboration program, directing all development and implementation efforts for solutions for application and information access and protection. Exostar's cloud-based identity and access management and business-to-business collaboration solutions bring together over 75,000 individuals in more than 1300 manufacturing, CRO, laboratory, and academic organizations worldwide. Mr. Johnson earned his BS in Industrial Engineering from Georgia Tech University.

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External Delivery

The Big Hack Attack

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

About 2 weeks ago, I read a book on hackers and the damage they can do to a business. The author said two things that really made an impression on me. The first is that it is not a matter of IF your business is going to be hacked but WHEN your business is going to be hacked. The second thing he said was that the vast majority of businesses in the US do not have any plans for what to do if they are hacked.

In the event that you are hacked, do you know what to do, who should be involved, and who is in charge? Do you have a Disaster Recovery Plan and a Business Continuation Plan? If your answer is no, then please read on.

Let's look at a hypothetical company by the name of ABC Company that is hacked. On May 1, one of the IT people, who is working overnight, discovers that the company website is acting strangely. Every 3 seconds the company receives an email with an Emoji on the subject line and nothing else. This is critical because the company conducts all of its business through its website.

The CIO (Chief Information Officer) was away on a business trip but was contacted in the middle of the night at her hotel and apprised of the situation by the IT person. The CIO asked the person in IT if he knew where the book was with the company emergency procedures for this type of situation.

The IT person answered that he did not but maybe the head of IT did. The CIO told him to get in touch with her ASAP. The IT person answered that he could not because she was on vacation and he did not know where.

The CIO began making phone calls to the CEO, COO, VP of Operations, VP of Sales and Marketing, the Director of Communications, and other key people to schedule a conference call to discuss an action plan within the hour. That conference call took more than 2 hours to put together, and when it finally took place, it was a waste of time.

Because there was no plan, everyone had his or her own opinion as to what to do, and the dysfunctional conference call ended with no decision. So they just pulled the plug on the website and put up an "under construction" notice in its place.

Had the ABC Company developed Disaster Recovery and Business Continuation Plans, the company would have known exactly what to do, who was to do what, who was in charge, and where the employees should relocate to if their building was inhabitable or there was no power there.

The point of this article is to make you aware of the strong possibility that your company will be hacked and when that happens, you should be well planned out as to how to keep your company running while the problem is fixed. ◆

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