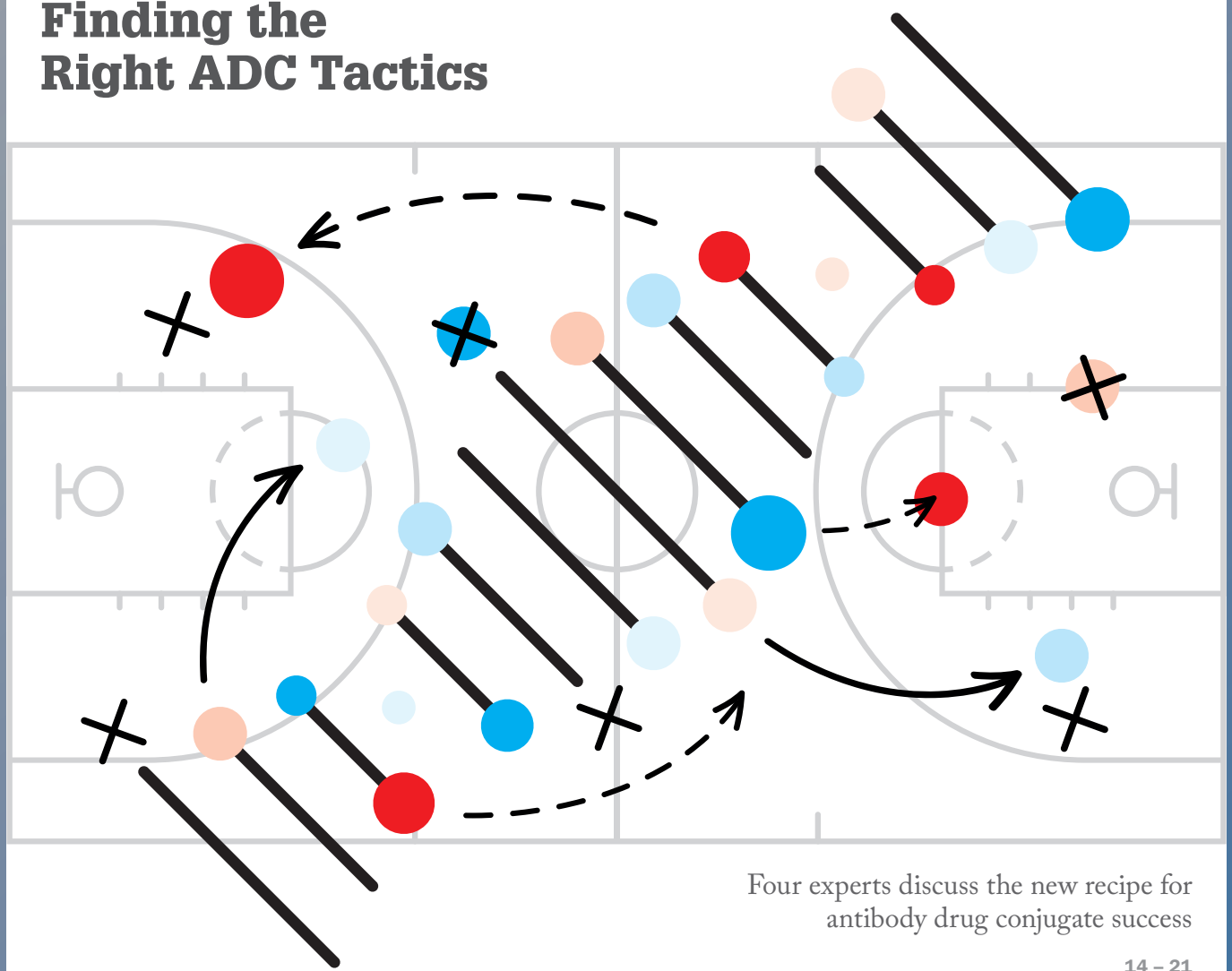
JULY / AUGUST 2023 # 92

the Medicine Maker®

Finding the Right ADC Tactics



Four experts discuss the new recipe for antibody drug conjugate success

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The Battle Outside Raging

Climate change is real – it's happening now – and it will take an awesome effort from the pharma industry to mitigate it

It is difficult to ignore the increasing adverse weather events disrupting lives all over the world – though many try. From flash floods in Germany to rain-related landslides in India, Rwanda, and the DRC. And from winds speeds of up to 111 mph in Australia to wildfires recorded in Greece, Hawaii, Canada, and Tenerife. The weather is changing, whether we're prepared to attribute this to anthropogenic climate change or not. Given that the global pharmaceutical industry has such a broad footprint across the planet, it is only a matter of time before these events catch up with serious consequences.

Case in point: in July, a tornado tore open one of Pfizer's storage facilities in North Carolina, causing supply chain disruptions for customers dependent on fentanyl and anesthetic lidocaine. Fortunately, the damage was minimal and largely superficial, and – most importantly – nobody was hurt. Yet, this particular event should serve as a warning to pharmaceutical industry players – even the big ones – that any vulnerabilities that do exist must be addressed and that measures must be put in place to keep supply lines open, resilient, and responsive.

Not every victim of extreme weather events is so fortunate; lives have been lost and many, many properties have been damaged or destroyed in all the places listed above – and beyond. It is clear to me that the pharmaceutical industry is well-placed to help restore some of the damage done, and also save lives through the rapid mobilization of medicines and other resources. Indeed, credit is due to Bayer for having done just that. To assist in the relief efforts ongoing on the island of Maui, Hawaii, Bayer made a cash donation of $250,000 alongside a matching amount of essential healthcare products, such as aspirin, antihistamines, and antibiotics.

Philanthropy is a powerful reactive tool to have in one's resources, but to proactively mitigate the consequences of climate change requires something more – far more – than pharmaceutical industry players can provide alone. I'm well aware of the awesome power of collaboration in and across the industry for innovation and production purposes, but the times they are a'changing; the battle outside raging will soon shake your windows and rattle your doors, as Bob Dylan prophesied. So let's use that awesome power and those incredible resources to make the change work for people and the planet.

Rob Coker
Deputy Editor

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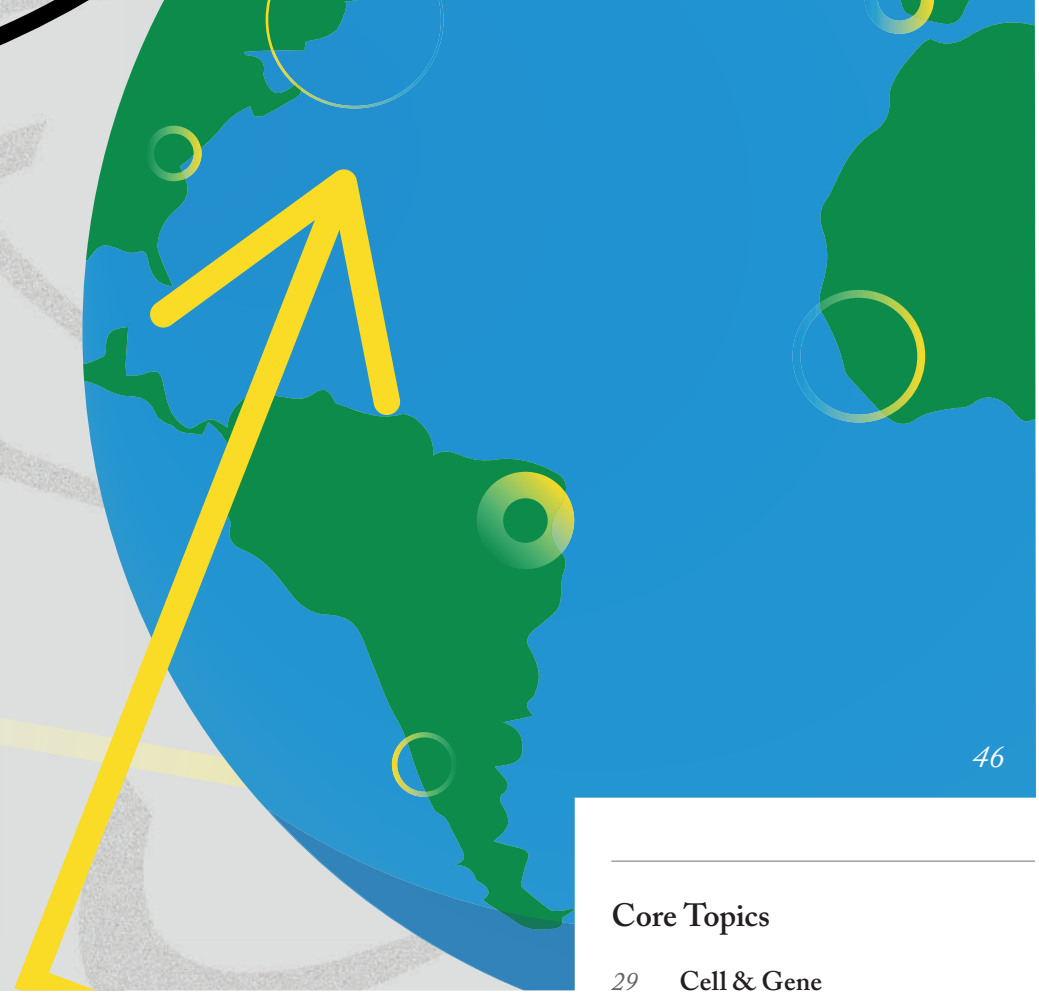
Getting the strategy right for the success of ADCs



NextGen

Best Practice

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Sitting Down With

the Medicine Maker

ISSUE 92 - JUL / AUG 2023

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Distribution: The Medicine Maker (ISSN 2055-8201), is published bi-monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK. Single copy sales £15 (plus postage, cost available on request info@themedicinemaker.com). Non-qualified annual subscription cost is £110 plus postage

The ADHD Video Game – for Adults

Akili Interactive releases video game for adults to treat ADHD

In 2021, EndeavourRX (developed by Akili Interactive) was launched on prescription in the US after being approved by the FDA for children aged 8 to 12 with ADHD (1). Now, EndeavourOTC is available for adults in the US from the Apple App Store. The game uses a subscription plan, with prices from $10 per month, and players are encouraged to play every day for six weeks.

Using the company's Selective Stimulus Management Engine (SSME) technology, the game encourages players to multi-task whilst filtering out distractions. Players must tap specific stimuli while ignoring others, and simultaneously navigate through a course to avoid obstacles. "Doing both of these at the same time uniquely challenges and alters pathways in the brain, boosting attention and focus," states the game's website.

According to Akili Interactive, increasing numbers of adults are reportedly seeking help for ADHD symptoms, including inattention and lack of focus. At the same time, there are shortages of the ADHD medication Adderall in the US. A statement from Akili Interactive says, "As the gap between demand for care and availability of effective treatments widens, Akili released EndeavorOTC under FDA's enforcement policy established shortly after the onset of the COVID-19 pandemic to facilitate rapid access to certain low-risk, mental health-related digital health devices."

In May, Akili Interactive published results from a clinical trial involving adults with inattentive or combined-type ADHD (2). According to a statement, "Nearly three-quarters (72.5%) of adults reported at least some improvement in their quality of life as measured by the validated Adult ADHD Quality of Life Scale (AAQoL), and nearly 50 percent (45.8%) of adults met a prespecified threshold for clinically meaningful improvement."

Akili Interactive says it will submit the data to the FDA for official approval.

References

1. *The Medicine Maker, "The Story Behind Akili Interactive's FDA-Approved Video Game," (2022). Available at: https://bit.ly/45l2JsZ.*
2. *Akili Interactive, "Adults with ADHD See Significant Improvements in Attention, ADHD Symptoms, and Quality of Life in Clinical Trial of Akili's EndeavorRx Video Game-Based Therapeutic," (2023). Available at: https://bit.ly/3QvEpAi.*

TIMELINE

A Timeline of Drug Development for Alzheimer's

It's been a busy few years for failures and successes in Alzheimer's drug trials. Here's a reminder of some of the highlights

2012

Pfizer and J&J scrap development of bapineuzumab after failed trials

March 2019

Trials of Biogen and Eisai's aducanumab halted due to poor results

October 2019

New analysis of aducanumab phase III appears to show promise

July 2020

Aducanumab submitted for FDA review

June 2021

FDA approves aducanumab under accelerated approval pathway – despite advisory committee voting against the drug

December 2021

EMA refuses marketing authorization for aducanumab

BLOGS - IN-BRIEF

Our blogs provide a full breakdown on topical issues in science, medicine, and pharma. Read the full articles on our website.

- In 2003, Kathleen Folbigg was sentenced for killing her four children over a 10-year period. She was accused of smothering the babies, who all died suddenly aged between 19 days and 18 months. In June 2023, a full pardon was signed and she was released – because of revelations brought about by genetic research. As part of an inquiry into the case, scientists were asked to investigate whether there could be a genetic cause for the deaths of the children. The results could open up a discussion on genes that contribute to sudden infant death syndrome. *tmm.txp.to/blog-SIDS*
- An EMA Safety Committee is assessing whether GLP-1 receptor agonists Ozempic, Wegovy, and Saxenda (all made by Novo Nordisk) are linked with increased risk of suicidal thoughts and thoughts of self harm. In the EU, suicidal behavior is not listed as a side effect for any of the drugs, but labelling in the US is different. The review is expected to conclude in November 2023, with the EMA analyzing around 150 reported cases of suicidal thoughts and self harm relating to the drugs. In this blog, we ask exactly how and why medicines can trigger suicidal thoughts. *tmm.txp.to/blog-suicide*
- Cosmonaut and International Space Station flight engineer Dmitri Petelin recently conducted the latest in a long, long string of experiments involving hair and saliva samples to learn more about the effects of microgravity on the human immune system. In 2022, fellow cosmonauts Denis Matveev and Sergey Korsakov performed similar experiments, as did British astronaut Tim Peake back in 2016. The topic of medicines in space may not have exactly blasted off, but it does seem to be getting off the ground. This blog examines studies in the area and what we know about how microgravity affects the immune system. *tmm.txp.to/space-based-medicine*

Honey, I Shrunk the Molecules

Does microRNA-132 have therapeutic potential against Alzheimer's disease?

Scientists from the Netherlands Institute for Neuroscience and the VIB-KU Leuven Center for Brain and Disease Research have shown that microRNA-132 can affect different brain cells, with potential implications for Alzheimer's disease (1). Despite their small size, microRNAs can exert significant influence by binding to RNA molecules, subsequently affecting gene and protein expression. Disrupted microRNA profiles are commonplace for patients with Alzheimer's disease – particularly, when it comes to microRNA-132. Notably, their research revealed that microRNA-132 also influences microglia and affects neuroinflammation. Increasing microRNA-132 levels in microglia prompts a shift towards a healthier state, potentially influencing disease-associated changes. The researchers suggest that other neurodegenerative disorders also exhibit a decrease in the same microRNA, which means their findings could translate to a broader spectrum of diseases and conditions.

Reference

1. *H Walgrave et al., iScience, 26, 6, (2023). DOI: 10.1016/j.isci.2023.106829*

April 2022

CMS set strict criteria for covering amyloid plaque targeting mAbs

EMA filing for aducanumab scrapped

September 2022

Positive phase III results for Biogen & Eisai's lecanemab

January 2023

FDA approves lecanemab under accelerated approval pathway

January 2023

Marketing authorization for lecanemab submitted to EMA

FDA complete response letter for Eli Lilly's donanemab

May 2023

Positive phase III trial results of donanemab

July 2023

FDA grants traditional approval for lecanemab

Credit: Shutterstock.com

Remote Controlled Chemo

Meet MAPSULES: nanocapsules that deliver targeted chemotherapy to solid tumors

Scientists and medical practitioners worldwide continue to investigate drug delivery methods that can improve treatment outcomes in cancer. Nanotherapies were once hailed as a promising approach to mitigate chemotherapy side effects, but they have fallen short in delivering desired nanoparticle concentrations to solid tumors. However, researchers have rekindled hope by capitalizing on tumor-specific structures. Their solution involves the development of biodegradable magnetoplasmonic nanocapsules, known as MAPSULES, which can effectively eradicate tumors via remote-controlled delivery of potent chemotherapy to targeted tumor sites (1).

Their study demonstrates the positive therapeutic effect of MAPSULES in mice models of human breast tumors. MAPSULES not only boosted drug action but also minimized damage to surrounding tissue. Indeed, in vivo trials revealed that tumors were successfully eliminated through intravenous administration at a concentration between 200 and 500 times lower than its therapeutic window.

Results also showed that laser irradiation of MAPSULES could increase therapeutic impact by generating heat locally in the tumor site. How? According to Borja Sepúlveda, researcher at Instituto de Microelectronica de Barcelona and the study's principal investigator, the metallic iron nanolayer takes advantage of its plasmonic behavior to very efficiently absorb near-infrared light, which has a high penetration into tissues. Using this combination, the researchers can magnetically increase the concentration of nanocapsules in the tumor and amplify the therapeutic effect of the encapsulated drug using an external laser. After the external actuation, the nanocapsules degrade quickly, avoiding problems of bioaccumulation and toxicity.

The findings introduce the first design of a full nano-scale carrier containing large doses of chemotherapeutics with a thin external metal coating. "Creating an 'Iron Dome' of sorts for cancer, MAPSULES not only kill cancerous cells, but also protect the patient from unnecessary damage to healthy tissue, thus augmenting cancer treatment outcomes," says Ofra Benny, researcher at the Hebrew University and study co-author. "With our discovery of MAPSULES's efficacy, we can advance our solutions and offer a wide range of materials that can be manipulated and activated remotely to support a wide variety of therapies for diseases beyond cancer."

Reference

1. *A Fluksman et al., ACS Nano Journal, 17, 3 (2023). DOI: 10.1021/acsnano.2c05733*

Secrets of the Super Dodgers

Could a genetic advantage explain why some people don't get sick from SARS-CoV-2?

From the start of the pandemic, researchers have been trying to uncover why some people get sick from SARS-CoV-2 and others do not. A study led by UC San Francisco believes that a gene mutation may be the culprit (1). Their findings focus on human leukocyte antigen (HLA). Studying almost 30,000 participants, the research team found that asymptomatic individuals were more likely to carry the HLA-B*15:01 allele than symptomatic participants; specifically, 20 percent of individuals who remained asymptomatic after infection carried HLA-B*15:01, compared with only nine percent of those who experienced symptoms. Those who carried two copies of the allele were over eight times more likely to remain asymptomatic than those with other genotypes. According to the researchers, people with HLA-B*15:01 had T cells that were poised to attack SARS-CoV-2 – facilitating a rapid immune response that stops people from developing symptoms.

Reference

1. *DG Augusto et al., Nature, 620, 128 (2023). DOI: 10.1038/s41586-023-06331-x*

IMAGE OF THE MONTH

Off-World Oncology

The International Space Station (ISS) National Laboratory is collaborating with NASA to advance disease research in space. In this image, NASA astronaut Peggy Whitson – the American record holder for spending the most days in space – is investigating cancer aboard the ISS.

Credit: Image courtesy of NASA

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QUOTE of the month

"Clearly nature is strong. So too is ingenuity and the human spirit. A great deal of work needs to be done, but I assure everyone, most importantly the people of the Rocky Mount community, that we will put Pfizer's full power behind this effort."

This was the response of Albert Bourla, Chairman and CEO of Pfizer, after a tornado ripped through their Rocky Mount facility in North Carolina on July 19.

Credit: Shutterstock.com

The Realities of Herbal Remedies

How scientists extracted a treatment for episodic ataxia from traditional Kwakwaka'wakw medicine

Traditional Kwakwaka'wakw First Nations remedies have shown promise in treating type 1 episodic ataxia, an autosomal dominant hereditary condition characterized by muscle spasms and impaired coordination (1). They reportedly ingested ninebark root extract, rubbed bladderwrack kelp on the affected limbs, and placed nettles on the soles of the feet after cutting with sharp seashells. And the approach seems to work. A research team applied extracts of the plants to cloned human Kv1.1 channels, including those carrying EA1 mutations, expressed in frog oocytes, and recorded the effects on channel activity using electrophysiological techniques. Two compounds in these plants – tannic acid and gallic acid – were of particular interest because each is able to rescue activity of the EA1-linked mutation-carrying ion channel proteins. The team has now designed a mouse model of a relatively severe form of human EA1 to test the safety of gallic acid and whole plant extracts.

Reference

1. *RW Manville et al., Nature Communications, 14, 3281 (2023). DOI: 10.1038/s41467-023-38834-6*

In My View

Experts from across the world share a single strongly held opinion or key idea.

To Be Precise

With more and better data comes new advances, specifically in our knowledge of individual genetics. Here's how pharmacogenomics research will accelerate precision medicine initiatives.

By Neil Ward, Vice President at PacBio, EMEA

Personalized or precision medicine has long been touted as the future of healthcare. Indeed, some precision approaches are already being used to improve patient outcomes – for example, blood and organ typing to reduce the chances of rejection. It is also increasingly common to take a person's individual genetic variation into account when making clinical decisions. This personalization trend is driving research into many other disciplines, with pharmacogenomics (PGx) being one area of particular promise. PGx analyzes an individual's genetic makeup to determine how they may respond to a certain medicine – but research has also shown that genetic testing can reduce adverse reactions to drugs by nearly one third.

As well as direct patient benefits, PGx holds additional interest because of the hundreds of millions of dollars that are, to put it bluntly, wasted each year administering ineffective medicines. A 2022 study from the Royal College of Physicians and British Pharmacological Society demonstrated the potential of pharmacogenomics to reduce ineffective prescribing, identifying that the commonly prescribed pain relief drug codeine is not effective in around eight percent of the UK population because of their underlying genetic predisposition. Conversely, there are a small number of people who have multiple copies of CYP2D6 that rapidly convert codeine into morphine, which in rare circumstances can lead to drug overdoses.

Already in Europe, we are seeing several countries trialing the use of PGx to support clinical decision making and improve patient outcomes. And PGx guidelines exist for several drugs on the market – with some medicines even requiring genetic testing before they can be prescribed. And, more broadly speaking, use of PGx in a clinical setting is still relatively low.

It's also clear that there are many more genetic variants to discover – and that's no easy feat. Identifying the genetic variations that can be used as pharmacogenomic markers is a complex process, requiring highly accurate, in-depth sequencing of the genes associated with drug response. Though some variation is straightforward to capture using less advanced technologies, such as short-read genetic sequencing (where DNA is broken into small pieces for analysis), certain genes are too complex or far apart to be captured, and multiple assays must be run to adequately understand difficult genes.

One such example is the aforementioned gene CYP2D6, a widely-studied PGx gene found to directly impact the metabolism of around 20 percent of the most prescribed medications – including cancer drugs, opioids and antidepressants. Because of high levels of polymorphisms and structural variants, CYP2D6 is particularly challenging to study.

"In Europe, we are seeing several countries trialing the use of PGx to support clinical decision making and improve patient outcomes."

There are over 130 defined haplotypes of CYP2D6 known to impact drug metabolism, but relying on short-read sequencing to detect actionable variants is not sufficient. A comprehensive picture of a person's genome is required to ensure that rare or novel haplotypes, which might change how they respond to drugs, are not missed. In such a cases, highly accurate long-read sequencing is necessary to identify PGx markers and difficult-to-sequence pseudogenes, as well as structural and complex variants.

The good news for researchers is that with long-read technologies now faster, more affordable, and more accurate than ever before, whole-genome sequencing is increasingly accessible. Such highly accurate long-read sequencing will accelerate precision screening programs and support clinical prescribing decisions, ultimately reducing inefficient prescribing costs and improving patient outcomes and experiences.

In short, I believe we are entering a new phase of precision medicine and, with advances in genome sequencing technologies, we can expect to see pharmacogenomics also move to the next level.

Ode to the Microbe

Understanding the role of microbial fermentation in the supply of the DNA template, RNA polymerase, and enzymes used in purification of mRNA vaccines

By Kyle Probst, RD&A Senior Scientist at Kerry

After decades of development and promise, the COVID-19 pandemic brought mRNA vaccines to the forefront of immunization technology. Compared with other vaccine technologies, mRNA vaccines are fast to develop, quick to modify in response to new variants, and less costly to produce. The cell-free manufacturing process is endorsed as a safer and simpler option compared with existing vaccine technologies that rely on growing and culturing microbes and viruses; some of which are infectious and potentially hazardous (1). However, we should not overlook the fact that many of the raw materials required for the cell-free process of mRNA vaccines are derived from cells – using microbial fermentation to be specific.

The manufacture of mRNA vaccines uses a biochemical in vitro transcription (IVT) reaction. The DNA template that encodes the antigen, RNA polymerase,

and nucleic acids are combined under the proper conditions to transcribe the mRNA. Post-transcription capping and tailing is performed by RNA modifying enzymes to improve mRNA stability and protect against degradation. The target mRNA molecule is then purified and encapsulated in a lipid nanoparticle to stabilize and allow for uptake once administered.

"Many of the critical raw materials used in the IVT process are produced from microbial fermentation."

Many of the critical raw materials used in the IVT process are produced from microbial fermentation. The DNA template is produced in microbes from plasmids. The enzymes used for the IVT reaction – RNA polymerase, RNA modifying enzymes including guanylyl transferase, 2'-O-methyltransferase and poly-A polymerase – are also produced in microbes. Even the processing aid DNase, used to remove non-target DNA during purification, is produced via microbial fermentation.

Microbial fermentation is described as the use of microbial cells to generate energy and facilitate biochemical reactions. Like microscopic factories, the cells convert nutrients, such as glucose (carbon), peptones (nitrogen), and minerals into energy and building blocks to make important products of interest. Strain improvement techniques and genetic modification strategies, such as recombinant DNA transformation, have birthed an entire bioindustry that uses microbial hosts to manufacture biological molecules at large scale. By cloning foreign DNA in cells, microbes like Escherichia coli, Saccharomyces cerevisiae and Pichia pastoris can be reprogrammed to make molecules in high quantities in an economical and sustainable manner. Insulin, somatropin (human growth hormone), and the aforementioned DNA templates for the SARS-CoV-2 mRNA vaccines are all made using genetic transformation.

Genetically engineered E. coli is one of the most important industrially relevant microbial hosts. First used for DNA cloning back in the 1970s, it is well studied, robust to industrial conditions, and easy to genetically modify (2). Most commercial E. coli strains are descendants of two isolates, K-12 and B. These isolates have been improved through genetic alteration to create strains for specific purposes, including cloning DNA and expressing proteins. In addition to the strains, the design of the DNA vector or plasmid used to genetically modify the cells is an equally important consideration.

To produce plasmid DNA for mRNA vaccines, E. coli strain and vector combinations are chosen to yield high copies of the plasmid. E. coli DH5α, a K-12 derivative, is better suited for DNA plasmid production because it lacks the genes for endonuclease 1 (endA) and DNA repair protein (recA) to increase plasmid yield and stability. Plasmid vectors used for mRNA vaccines often include bacterial sites of origin for high copy amplification in E. coli and a eukaryotic region to express the antigen once administered into the host cell.

For the enzymes used in the IVT process, E. coli BL21 (DE3), a B-strain derivative, is often used. It has been genetically modified to carry a chromosomal copy of the T7 polymerase, which allows for faster RNA transcription and ultimately greater enzyme or protein expression. Additionally, BL21 strains are deficient in two proteases, Lon and Ompt, which help minimize protein degradation during purification. Plasmid vectors for protein production often contain an inducible promoter to "switch on" expression. One example is the Lac promoter under the control of lactose or lactose derivatives (for example, isopropyl β- d-1-thiogalactopyranoside, IPTG). When added to the growth medium, IPTG induces the cells to produce the target protein of interest. Protein expression is metabolically demanding; thus, inducible promoters help fine tune the timing of expression to shorten lag times and increase productivity.

In summary, microbial fermentation plays an important role in the manufacture of mRNA vaccines. Looking ahead, I believe that new technologies, such as cell-free systems and the IVT process, will be increasingly sought after to meet the demands of the ever-burgeoning bio-based economy. But it's also clear that cell-dependent approaches will continue to play a crucial role in manufacture of mRNA vaccines, gene therapies, and other genetic medicines.

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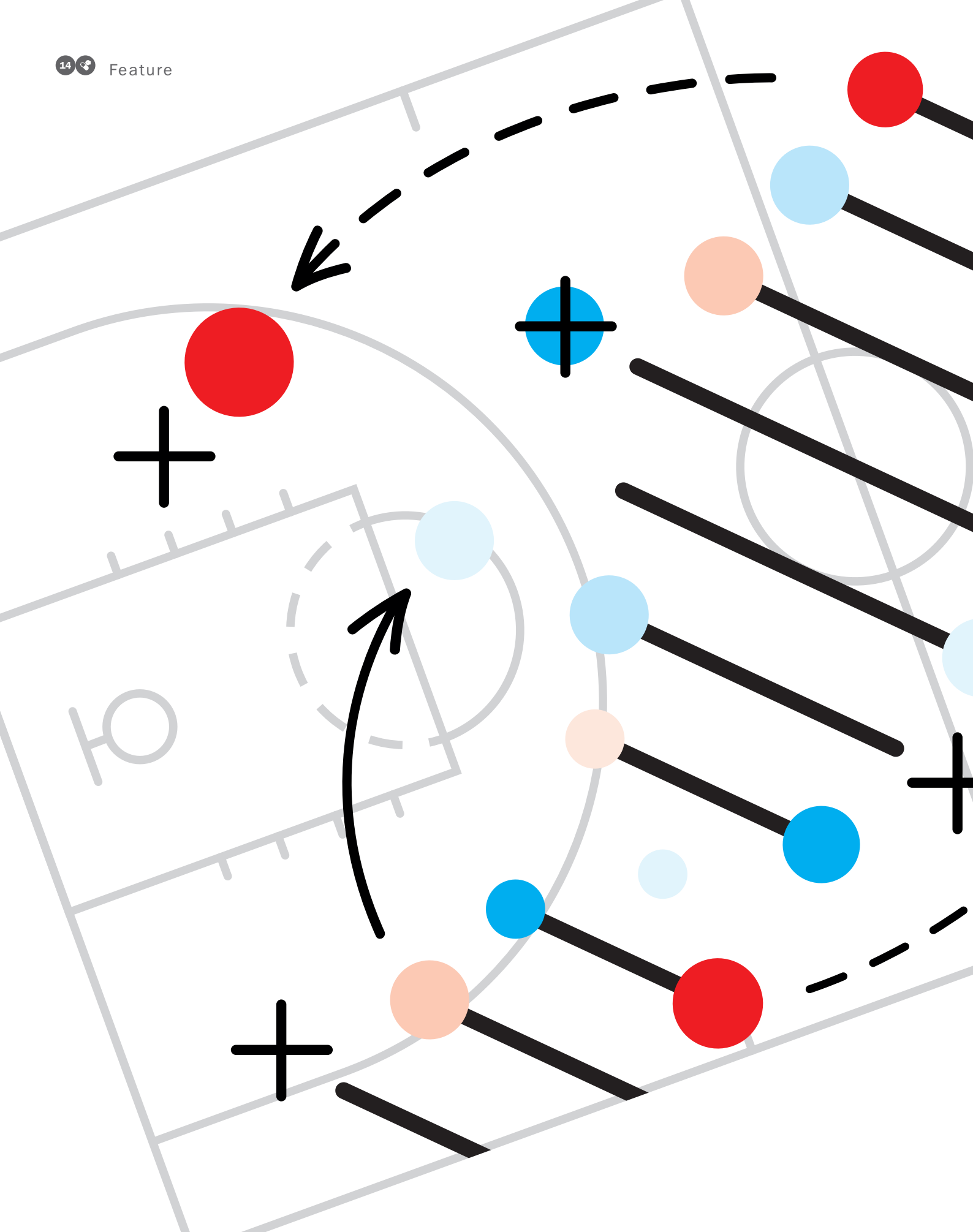


REVENGE OF THE ADCS

Are antibody drug conjugates (ADCs) finally about to live up to the "magic bullet" hype in cancer treatment?

From complex design challenges to issues with linker stability, ADCs have faced many hurdles, but recent developments suggest we may be at a turning point. We ask four gurus if the time for ADCs has arrived – and what advancements are paving the way for their success.

Is the term "magic bullets" a fair description of ADCs?

Zhang: This description may not be completely fair because of the difficulties of delivering both safety and efficacy with previous ADC technologies. ADCs are designed to be highly targeted therapies that deliver a potent cytotoxic payload directly to cancer cells. In other words, they are a "targeted chemotherapy."

However, these treatment modalities are only as good as the conjugation method that holds the chemotherapy and the antibody together. For example, ADCs that have unstable conjugation can prematurely release their toxic payload, which can damage healthy tissues, increase drug resistance potential, and deliver inadequate amounts of the cytotoxin to the tumor. Ultimately a "magic bullet" would have sufficiently stable conjugation technology to enable robust on-target delivery of cytotoxin to cancer, with minimal off-target effects to the patient.

Spycher: I actually do think that "magic bullet" is a fair description of ADCs. By combining a highly specific antibody with a powerful anti-cancer drug to target and eradicate tumors, we can potentially eliminate unwanted side effects in other parts of the body. With ADCs, we are attempting to deliver the anti-cancer drug in the most targeted manner possible, thereby avoiding the toxicities we often see with traditional cancer therapeutics. Over the years, there have been some development challenges that have prevented ADCs from reaching that "magic bullet" potential, but the field is in a good place now to start seeing results in practice.

Robinson: Paul Ehrlich's "magic bullet" term has been thrown around for more than a century, and encapsulated his vision that "we need to learn how to aim chemically." In other words, Ehrlich saw an opportunity to target chemotherapeutic agents to receptors present on disease-causing agents rather than healthy tissues, thereby improving the therapeutic window of those drugs. In many ways, the modern ADC can be seen as the realization of his theory.

Pinkas: Based on clinical data from numerous ADCs over the past few decades, I feel that a better description could be that ADCs represent a validated approach for "targeted payload delivery."

Philipp Spycher

Why has it taken so long for the field of ADCs to take off? And are we finally at a turning point?

Zhang: ADCs have been a promising class of targeted cancer therapies for over 20 years, but their development has been challenged by several factors. One key challenge has been the complex nature of ADC design, which requires the combination of a cytotoxic drug, an antibody, a linker, and the conjugation technology that connects the components. Each of these components must be optimized in different ways depending on the cancer types or targets. It can take years to develop an ADC with the desired therapeutic profile.

The Gurus

Shawn Zhang, Chief Scientific Officer, Ambrx Biopharma
Philipp Spycher, Co-founder and CEO, Araris Biotech
Matt Robinson, Chief Technology Officer, Immunome
Jan Pinkas, Chief Scientific Officer, Pyxis Oncology

Despite these challenges, recent advancements in ADC technology have renewed interest in the field. For example, the development of site-specific conjugation technologies has enabled the creation of more precise and stable ADCs, reducing off-target effects and increasing the concentration of the "magic bullet" available to reach tumor sites. In fact, there are a number of promising ADCs now in late-stage clinical trials, as well as plenty more in preclinical development.

Spycher: Tremendous leaps have been made in ADC technology over the last 30 years, and these drugs now have the potential to be highly efficacious cancer therapeutics. However, their limited therapeutic window has been a cause of contention in clinical development (i.e., the balance between clinical efficacy in killing tumor cells and tolerability profile), which explains the lack of broader adoption at the expected pace. Additionally, poorly designed linkers that connect the highly toxic drug payload and the antibody can lead to the inability to efficiently deliver the drug payload to the tumor, thus preventing tumor eradication, or a premature release of the toxic drug in the bloodstream, leading to unwanted toxicities in healthy tissues.

There have also been issues with aggregation of ADCs, which can decrease binding of the molecule to the antigen and shorten half-life in the blood. Finally, existing technologies pose challenges of high cost and time to manufacture. With new ADC technologies being developed as well as increased interest in the space, I believe we're at a turning point for the field to take off.

Robinson: Realizing Ehrlich's vision has not been simple for many reasons. ADCs are large, complex molecules whose activities are dictated by a number of different parameters, including 1) selectivity and overall uptake of the antibody into tumor versus normal tissues; 2) stability of the ADC in patients; and 3) potency and mechanism of action of the cytotoxic agent being used. Lots of work has gone into understanding how best to attach cytotoxic agents to the antibody delivery vehicles in a way that provides the necessary improvement in therapeutic window versus free drug. In my opinion, the advances made in those areas over the last 10 years or so are what have led to the resurgence in the ADC field.

Pinkas: The ADC field is entering an exponential phase of growth. As the others explained, the technology has taken time to mature because of its complex design and manufacturing when compared with traditional therapeutics. ADCs use payloads that are upwards of 100 times more potent than traditional chemotherapeutics with highly specific antibodies that target and release the drug at the right location. The entire process is a balancing act between safety and activity. Over time, payloads with distinct mechanisms of action have tuned potency, conjugation strategies have become more precise, and linkers have been developed that are more stable in circulation. The improvement of these technologies may yield a new generation of ADCs that will truly transform the cancer treatment landscape.

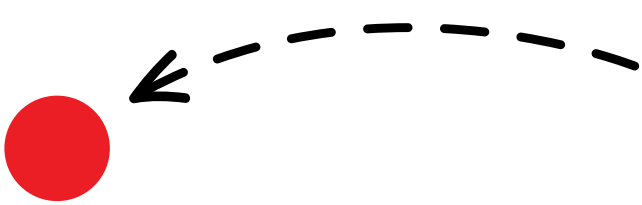
What have been the biggest milestones for the ADC industry as a whole over the past two years?

Zhang: Currently, there are 12 ADCs approved by the US FDA, the most recent being Elahere in 2022 for ovarian cancer and Tivdak for cervical cancer in 2021. I think that one of the key milestones is yet to come – using ADCs to treat solid tumor indications. Most approved ADC therapies target liquid cancers, but there is increasing focus now on solid tumors.

Spycher: There have been encouraging investments from big pharma into smaller biotech ADC companies, including major deals between Seagen and Pfizer, as well as GSK and Mersana. Investment confidence in the space is very promising to see.

Robinson: In my opinion, the improvements in linker and conjugation chemistries developed over the last decade have enabled clinical successes that have led to multiple approvals in the space. Perhaps most notably, the approval of Enhertu for the treatment of breast cancer showed how the advances made in the ADC field can be leveraged to substantially improve upon earlier generation therapies and significantly change the standard of care in cancer treatment.

Pinkas: I agree; the approval of Enhertu in people with low expression of HER2 represented a critical moment for the field and showed us that ADCs could go beyond what was possible with traditional therapeutics, reaching more patients than previously thought possible. Moreover, Enhertu demonstrates that the potency of the payload is an important component to optimize and that payloads with the highest potency are not always the best.



What are the challenges and biggest discussion points when it comes to optimization?

Zhang: The utility of ADCs is significantly hindered by dose-limiting, off-tumor toxicities. Conjugation plays a critical role in controlling the stability, release rate, and efficacy of the drug payload, and instability within this can lead to premature drug release and toxicity, while linker stability can undermine drug release and efficacy. Therefore, pairing optimal linker design, conjugation chemistry, payload class, and tumor target characteristics is necessary to balance stability and release rate appropriately, and is an ongoing challenge in ADC development. Another challenge is achieving optimal antibody-drug ratio (DAR) and conjugation site selection. DAR is critical for maintaining the balance between efficacy and safety. By optimizing the site-specific conjugation of the cytotoxic payload to the antibody with the appropriate linker, then stability and homogeneity can be achieved, reducing dose-limiting, off-site toxicities.

Spycher: All ADC aspects require some optimization, but the optimization of the linker is really most crucial to the therapeutic. Linkers must be stable enough for the ADC to make it to the destination of the tumor without releasing the drug payload prematurely and causing off-target toxicities.

Robinson: The optimization process is highly dependent on how each company approaches ADC development. At my company, we believe it's important to keep the focus on novel targets that can enable selective tumor targeting and we have a discovery engine to help with this. Interestingly, our research is revealing novel target classes, such as proteins ectopically (abnormally) expressed on the surface of cancer cells, which we believe are uniquely tumor selective and potentially suitable for development as ADCs.

Pinkas: Conjugation chemistry is a hot topic right now. Historically, the process for assembling the components of an ADC was imprecise, which contributed to many of the toxicity issues. Today, companies are working on new strategies to approach conjugation in a site-specific manner to generate ADCs with more consistent DAR and to improve stability in circulation. Another major topic of conversation is bystander activity. The challenge with targeted therapeutics in oncology is tumor heterogeneity. All of the cancer cells within a tumor may not express the target, and consequently, treatments may be ineffective at completely eliminating cancer. One way around this is to improve bystander activity. Certain payloads, after being cleaved, can migrate to neighboring cells whether or not they express the target and exert their cytotoxic effect. Novel payloads with enhanced bystander activity have the potential to provide a more holistic antitumor strategy and could potentially lead to more durable responses.

"Tremendous leaps have been made in ADC technology over the last 30 years, and these drugs now have the potential to be highly efficacious cancer therapeutics."

What innovation is taking place in linkers?

Zhang: We are working on an expanded genetic code technology platform for incorporation of synthetic amino acids (SAA). Conjugation to the SAA enables the incorporation of an optimized linker-payload at any selected site in the antibody using industry standard cell lines, thus allowing for the generation of engineered precision biologics with site-specific, homogenous, and stable conjugation.

I'm also seeing the industry exploring a lot of new conjugation technologies, such as enzyme-based or sugar-based chemistries.

Spycher: It's been shown that in addition to stability of the linker being crucial for ADC success, linkers also play a role in clearance of the ADC. Some of the first innovations used labile and hydrophobic linkers resulting in poor efficacies, pharmacokinetic ADC profiles, and ultimately limited tolerabilities. At my company, we're working to create hydrophilic and highly stable linkers that allow for straightforward conjugation of the payload drugs, taking off the shelf antibodies and using them in our ADCs. We're able to retain the biophysical properties of the antibody thanks to the biochemical nature of the linker, which enables us to maximize exposure of the toxic drug to the tumor with only minimal toxicities. In addition, we believe that the release of the payload from the linker should be highly controlled in order to avoid excessive toxicities. For many conventional linkers, once the ADC gets internalizated in whatever tissues, the linker will be cleaved instantly which will then lead to a rapid payload release causing unwanted toxicities.

"While innovation is needed on all fronts, the biggest impact will come from improvements in conjugation strategies, since this can broadly translate to improvements across ADCs."

Robinson: History has taught us that each ADC is bespoke. From my perspective, the biggest advances in linkers are those that provide scientists with the ability to tailor attributes of the therapy, including but not limited to DAR, stability, site-specific conjugation, and solubility. Each of these can then be applied, in a coordinated way, to evaluate their contributions to the efficacy of newly developed ADCs.

Pinkas: Numerous advances have been made in linker chemistry to improve stability in circulation while maintaining efficient release in the tumor. Clinical data with ADCs comprising linker formats with a range of stability in circulation suggest that payload release contributes to toxicity. The concept of "cleavable" and "non-cleavable" linkers is outdated, and we should describe linkers based on their stability in circulation and the properties of the payload upon release in the tumor.

Where do you think the priorities should lie when it comes to furthering the ADC field?

Zhang: Based on current research and trends in the field, there are several priorities that can be considered, the biggest being improving the safety profile of ADCs. Approved ADCs such as Enhertu have shown promising results, but there is still a lot of room for improvement in terms of minimizing toxicity while maximizing efficacy. This can, and is, being done by further advancing site-specific conjugation technologies to improve the stability and homogeneity of ADCs and minimize off-target effects. In addition, some early research is exploring pro-drug approaches, where an ADC is largely inactive until it enters the tumor site, where it is activated by tumor proteases or other microenvironmental factors. I also believe research efforts should be directed towards understanding the mechanisms of resistance to ADCs and developing strategies to overcome them as well as understanding how they can work with other therapies in combination (i.e., checkpoint inhibitors, to produce the most effective treatment regimens).

Spycher: Further enhancing linker technologies that allow for fine tuning of stability and conjugation of the payload to the antibody should be at the forefront of ADC development. A strong linker foundation sets up the ADC for success, but I feel that linkers have been greatly undervalued in the ADC space. For example, depending on the amino acid sequence used for

the linker, potential dose-limiting toxicities can be much better controlled. In my view, there is no such story as a "one-size fits all linker." For each antibody and payload combination, linker optimization is necessary to maximize payload delivery to the tumor. Thus, linker performance sets the stage for the efficacy, safety, and tolerability of ADC therapeutics.

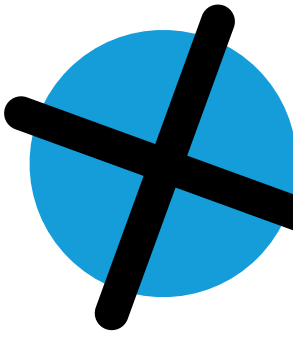
An additional consideration for the development of ADCs is the beneficial impact of high drug-to-antibody ratio (DAR). As we advance ADCs, we may find that high DARs are not necessary when using a low potency warhead. Ratios of 4 or less may be beneficial, and allow for high dosing and achieve high tumor penetration.

Robinson: While I believe future advances in linker, drug, and conjugation chemistry will continue to progress the ADC field, I also believe that a better understanding of the target landscape is going to be critical to fully realize Ehrlich's vision of the "magic bullet." Ehrlich postulated the need for receptors that are selective for disease versus normal tissues. The currently approved ADCs are focused on a small subset of targets, and hence small subset of cancers, with significant room to expand. The data we are generating at my company – through the interrogation of patients' antibody responses against their disease – has uncovered unique areas of biology that highlight novel target classes with the potential to provide increased tumor selectivity as compared to current targets. The better we understand those target classes, the more we will be able to select the right targets with potential to have the greatest benefit for patients, hopefully across multiple cancers.

Pinkas: While innovation is needed on all fronts, the biggest impact will come from improvements in conjugation strategies, since this can broadly translate to improvements across ADCs. The second priority is payloads. Not all payloads are created equally, and each employs a different mechanism of action, which may be more effective against certain types of cancers. Excitingly, newer payloads have been shown to induce immunogenic cell death, meaning that the drug kills the cancer cell and primes the immune system. This has major implications, especially in a combination treatment setting with other immuno-oncology drugs like checkpoint inhibitors.

Please make a bold prediction for the coming years…

Zhang: We will one day see ADCs replace standard chemotherapy treatment and become the standard-of-care for cancer treatment. With the approval of newer and more effective ADCs, and with the ongoing development of next-generation ADCs with improved targeting, potency, and safety profiles, the field is poised for significant growth. Additionally, as personalized medicine becomes more tailored as we gain a wealth of individualized data, ADCs with the ability to target specific cancer subtypes could become an increasingly important tool in the fight against cancer. This will include the identification and validation of new cancer targets, which would be invaluable for our field, industry, and most importantly, for patients with solid tumors who have long awaited consistently reliable treatment options.



Spycher: When looking at how ADCs have already altered the treatment paradigm for certain cancer indications, essentially re-defining how patients are treated and the impact on their quality of life, it seems to me that ADCs are primed to play key roles for many cancer indications. Eventually, they may replace conventional chemotherapy and live up to their initial promise of being "magic bullets."

Robinson: Leveraging modalities, such as ADCs, may provide a more linear clinical translation in drug development. I expect that a better understanding of cancer biology and the expression of targets on the surface of solid tumor cells, specifically in the context of the tumor microenvironment, will expand the landscape of tumor targets addressable by ADCs. This will lead to multiple clinical milestones and additional approvals in the coming years.

Pinkas: ADCs will become first-line treatments for many different indications. In oncology, we've seen the rise of many new treatment modalities, but we don't often see drugs breaking into first-line treatments. As the industry becomes more sophisticated in the design and development of ADCs, we'll start to see them become more prevalent first-line options.

Further down the road, I could envision ADCs being used outside of oncology. The beauty of this technology is that it's really a delivery system for highly potent small-molecule drugs. In fact, we could potentially apply this strategy to deliver different agents that, for example, suppress the activity of cells responsible for autoimmune disease.

A Call to Arms for Antimicrobial Resistance

Investment into new antimicrobial therapies has been lacking for decades – and we're now paying the price. We don't have enough drugs to fight the superbugs.

By Peter Jackson, Executive Director at Infex Therapeutics

Today, antimicrobial resistance (AMR) infections are killing more people than HIV or malaria. In 2022, a Lancet paper showed that around 1.27 million deaths were attributable to AMR; another 5 million deaths were associated with AMR globally in 2019 (1). By 2050, the annual number of deaths from AMR could be 10 million (2).

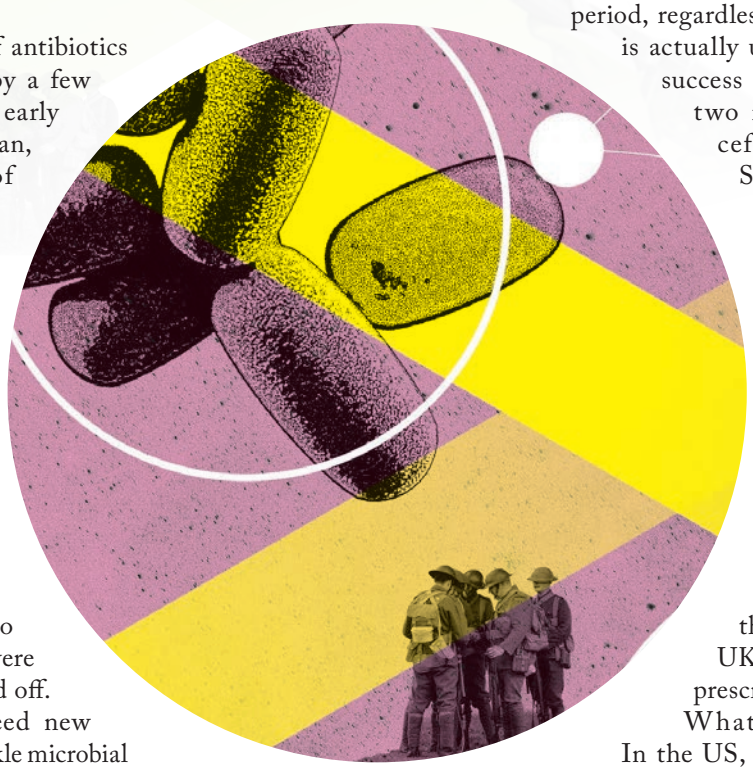
Frankly, we're in a bit of a mess. Resistance is increasing and we don't have enough new antibacterial drugs in the pipeline. A 2021 report from the WHO shows that there are only 77 drugs in the clinical antibacterial pipeline – and only 27 of those are for WHO priority pathogens (3). Compare this with the hundreds of drugs being developed for breast cancer and it's clear there is an imbalance.

The first penicillin resistant organisms were identified even before penicillin was first used. Bacteria reproduce at a rapid rate that massively outstrips our ability to develop new drugs to counter the evolution. Poor prescribing practices have not helped the situation. For a long time, antibiotics were handed out by doctors like candy, and, if a patient fails to complete the course or effectively clear a particular outbreak, there is the possibility for resistance to develop. Resistant organisms can pass from people to animals, from animals to people, and into the environment.

"The idea is to decouple the reward received by biopharma companies from the volume of drugs used by implementing a subscription model that pays a set price per year."

Where are all the drugs?

Big pharma's cessation of antibiotics R&D has been driven by a few different factors. In the early 1980s, the HIV crisis began, and a large amount of microbiological and drug development know-how pivoted from microbial infections to HIV. There have been massive successes in the treatment of HIV, of course, but too few resources pivoted back to microbial infections. With the original antibiotic drugs off patent, there was less money to be made, so manufacturing facilities were closed, repurposed, or sold off.



Fundamentally, we need new drugs to be launched to tackle microbial infections, but we don't want to use them – unless we absolutely have to. Biopharma's business model is to develop a new drug, prove that it meets an unmet need or is better than something that is already on the market, and then go out and sell as many doses as possible at the highest price possible. Given the increasing prevalence of AMR, however, there is no way that we want a valuable new drug that overcomes a particular resistance mechanism being widely used; all that will do is more quickly drive resistance to the new drug. We need money to be spent on development, and then we need to keep that drug on the shelf and only use it as a last resort. This approach completely disrupts the pharma industry's traditional economic model – and because biopharma companies and their investors are hugely rational people, they take the sensible decision to put all their money into cancer or other chronic diseases.

Let's talk about pricing reform

In the UK, there have been many discussions (which I have been involved in) about reimbursement reform to fund innovation in antimicrobial drug development. The idea is to decouple the reward received by biopharma companies from the volume of drugs used by implementing a subscription model that pays a set price per year over an agreed period, regardless of how much of the drug is actually used. Following the recent success of a pilot study involving two new antibiotics (Pfizer's ceftazidime-avibactam and Shionogi's cefiderocol), which paid £10 million per year over 10 years, the National Health Service (NHS) announced plans in July 2023 to expand this model to more pharmaceutical companies and roll it out across the whole of the UK. Under the new proposal, drug makers would receive up to £20 million a year for selling their novel antibiotics in the UK no matter how many were prescribed.

What about internationally? In the US, there was an AMR policy being prepared that had bipartisan support. However, it became mired in US partisan politics over other matters. Some elements have now been built into the Biden administration's healthcare bills, but it's still very frustrating that progress has been so slow. The COVID-19 pandemic hasn't helped the matter because it sucked all the resources and attention from other issues, including AMR.

The EU has a different set of problems; it is grappling with the balance of what needs to be done at the EU competency level, and what needs to be done at the member state level. Each member state has its own healthcare, reimbursement, and insurance systems. There are a lot of structural questions

and though the European Commission has published encouraging proposals, I can't see a permanent EU system being agreed quickly. Issues are still being debated, but we've already had multiple G7, G20, and UN meetings. Perhaps the forthcoming UN General Assembly High Level Meeting on AMR in 2024 will provide the focus needed to get difficult decisions made and these important measures across the line.

One interesting international initiative that is seeing success, however, is CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator), which is located at Boston University, and funded through a consortium of international governments and foundations, including the UK's Wellcome Trust. CARB-X helps support antibacterial projects through early development. Over the past year, it has helped eight projects progress to phase I and Ib trials. The idea is to help companies progress until they attract private support – but this private funding is not materializing and it all comes back to uncertainty about reimbursement. An investor once told me, "We understand the need, but we can't put a value on anything. We don't even know how these drugs will be paid for. How do we know what to invest and how are we going to get a return?"

We need to find ways to support these partnerships and the small and medium-sized enterprises (SMEs) involved. A great deal of the R&D effort for antimicrobial drug development has fallen on SMEs, but they often don't have the funds to move projects forward. The UK's Biotechnology and Biological Science Research Council (BBSRC) has invested over £100 million in fundamental science with research institutes and universities, but translational science into industry is happening slowly and at a small scale. Five years ago, there were only around 27 SMEs in the UK working on AMR and most of these only had 12 months-worth of cash. Further support for these SMEs is needed by more actively bringing together government funding, big pharma, philanthropic organizations and investors.

Again, in the UK, there is an effort to address this via the Infection Innovation Consortium (iiCON), which works with industry, academics, clinicians, and the NHS to support the development of anti-infectives right from concept to adoption.

A different kind of AMR strategy

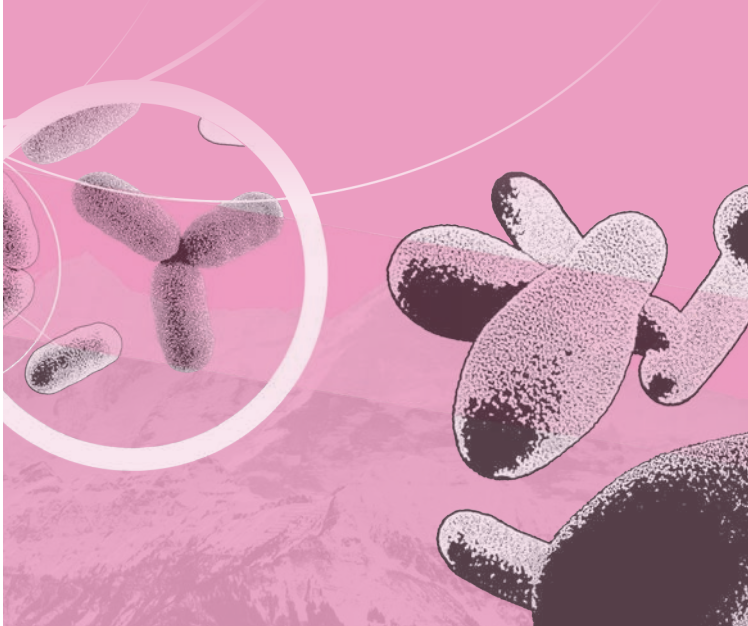
Putting politics aside for now, let's consider what is being done in terms of drug development solutions. We certainly need new antibiotics, but we shouldn't stop there; there are other drug development approaches that can combat AMR. It's all about innovation, innovation, innovation! I'd like to

The Beginning

My career in the UK started out in magnetic resonance imaging – and not on the medical side. Early in my career, I was involved in imaging stealth fighter wings. This was the height of Ronald Reagan's "Star Wars" program, which was supported by the UK's Margaret Thatcher, so there were a lot of exciting projects taking place. My friend at the time was involved in a project that sought to use high-powered lasers to blast holes in things… It was a curious time.

But I'm a commercial person at heart, so I ultimately ended up in general R&D management. From there, I got involved with the pharma industry. I was with Zeneca for a while (now AstraZeneca) but since then I've set up (and sold) several biotech companies. One of the most successful is Redx Pharma, which focuses on small molecules, fibrotic diseases, and cancer.

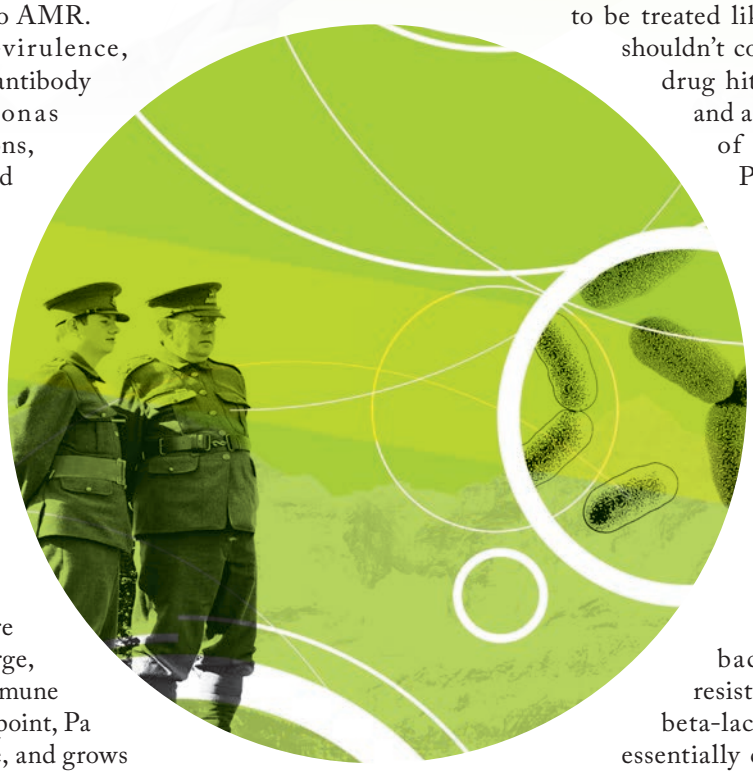
When AstraZeneca announced plans to vacate its Alderley Park site in the UK by 2016, local politicians were worried it could be a disaster for the region. Around the same time, the UK Government was calling for global action against AMR. Ultimately, the site was turned into a science park and is now home to a number of businesses – one of the first of which was the AMR Centre, which was created as a public-private partnership. Today, the AMR Centre is known as Infex Therapeutics and I am the Executive Director. I've also been involved in putting together a report that, in 2018, was used as evidence to inform the UK government's five-year (2019–2024) action plan for AMR. I was also proud to serve on the advisory group for the UK's antibiotic reimbursement trial.



"Here's a stark warning: If healthcare systems, politicians, investors, and the pharma industry don't fix the AMR problem, all other investments will be worthless."

share some information about two lead programs at Infex Therapeutics: RESP-X and MET-X. Neither of these drugs are antibiotics, but they are good examples of how creativity can be applied to AMR.

RESP-X is an anti-virulence, humanized, monoclonal antibody that targets Pseudomonas aeruginosa (Pa) infections, which have been identified by WHO as a critical threat to human health. Pa colonies hide inside a protective biofilm (which prevents antibiotics from reaching them) and are often found inside damaged lungs, such as those of bronchiectasis, COPD, and cystic fibrosis patients. The Pa colonies will be in a dormant state unless there is an opportunity to emerge, such as when a patient's immune system takes a dip. At this point, Pa switches to a virulent state, and grows a tail and a needle-injection mechanism. From a bioengineering perspective, it's fascinating. Pa's hollow needle can inject four different toxins. Pa can kill white blood cells – and patients with depleted immune systems will have very few of these around anyway – and use toxins to invade the lung tissue, causing invasive disease, which can also lead to sepsis. If a bronchiectasis patient gets colonized with Pa, it's bad news. With a moderate to severe infection, patients have a 40 percent four-year mortality rate. Consider that for a moment: Four out of 10 patients will be dead in the next four years.



RESP-X can be taken in a preventative fashion. An injection every month switches off the virulence mechanism of Pa so, even in a reduced immune state, the patient's immune system can better fight it off. The results in mice have been fantastic and we're now working on a phase I study with healthy volunteers. In April 2023, we reported a favorable safety and tolerability profile. If everything continues to work out, we'll then move to bronchiectasis patients who are long term colonized – and I really hope that we can give patients back a decent quality of life. If we can prevent the bacterial flare ups in these patients, we can avoid the use of antibiotics and slow down the emergence of AMR.

We've already spoken with some regulators who have indicated that a drug like this would not need to be treated like an antibiotic because it shouldn't contribute to resistance. The drug hits both antibiotic-resistant and antibiotic-susceptible strains of Pa by working around Pa's resistant mechanisms. This means that the drug should be reimbursable in conventional ways.

MET-X takes a different approach. It is a metallo-beta-lactamase inhibitor that targets Gram-negative Enterobacterales. At the start of 2023, it was awarded FDA Qualified Infectious Disease Product (QIDP) designation.

Over time, a number of bacteria have developed a resistance mechanism that uses beta-lactamases – enzymes that essentially chew up the chemistry on beta-lactam antibiotics. In certain bacteria, particularly Gram-negative bacteria, beta-lactamases sit between the outer and inner layers of the bacterial cell. For drugs to kill the bacteria, they have to pass through these layers, which means they will hit the enzyme – and become ineffective.

Beta-lactamases are divided into four different classes; three of which are serine beta-lactamases. There are a variety of drugs and drug combinations available that can work against these. Metallo-beta-lactamases, however, use zinc as a catalyst to degrade beta-lactam antibiotics – and there are few interventions. The pipeline is also very dry,

despite bacteria producing these enzymes being endemic in India and China – as well as in UK-based Southeast Asian communities. A few years ago, the UK saw an outbreak of klebsiella. A number of patients were treated with colistin, which is considered a last line of defence drug against multidrug-resistant Gram-negative bacteria. By the end of treatment, unfortunately half of the patients had died, and researchers identified colistin resistance in the bugs.

MET-X blocks the ability of bacteria to generate metallo-beta-lactamase. The drug itself isn't a treatment, but it does switch off production of the enzyme. If it were administered alongside a drug like meropenem – which usually metallo beta-lactamase would prevent from working – it would allow the drug to be effective. Essentially, we hope that MET-X will breathe life back into existing drugs.

We are hoping to start phase I trials soon. So far, we've done most of the work with meropenem, but we also have collaborations with pharma companies to look at combinations with other drugs to see if we can restore their efficacy too.

In my view, targeted therapies are needed to prevent widespread resistance. However, some companies are still focused on developing the next broad-spectrum antibiotic, even though payers will want to avoid using them widely to prevent further resistance. The old big pharma mindset of wanting to make the next blockbuster still persists in places.

Putting the issue front and center

Here's a stark warning: If healthcare systems, politicians, investors, and the pharma industry don't fix the AMR problem, all other investments will be worthless. If your cancer chemotherapy knocks the patient's immune system, the patient could die from an untreatable infection. Surgeries and wounds could be deadly. There is broad acknowledgement that AMR is a significant issue, but the problems are not being fixed quickly enough. I was involved in putting together a report in 2018 that was used as evidence to inform the UK government's five-year (2019–2024) action plan for AMR. The same issues highlighted in that report in 2018 are still present today – the recent expansion of the reimbursement reform by the UK's NHS is an excellent platform to change this situation but more needs to be done.

SMEs have done a lot of the heavy lifting, but they need help. I urge larger pharma companies to look at how to engage with the SME community – and to keep in mind that relatively small amounts of funding can make a big difference.

We also need to raise awareness amongst the general public so that they too can pressure politicians, who currently receive very little (if any) correspondence advocating for more funding for AMR. How can we raise awareness? In a recent consultation, I suggested that AMR should be included on patient death certificates, if it contributed to the cause of death, just as we did with COVID-19.

Public awareness could also help charities; Antibiotic Research UK receives less than £1 million each year in funding, whereas Cancer Research UK receives around £500 million…

Right now, not enough people are working on this global health issue. And that really needs to change. For the COVID-19 pandemic, there was an astonishing combined effort into developing and rolling out vaccines, with countries appointing COVID-19 task forces.

We need the same amount of effort to be dedicated to AMR.

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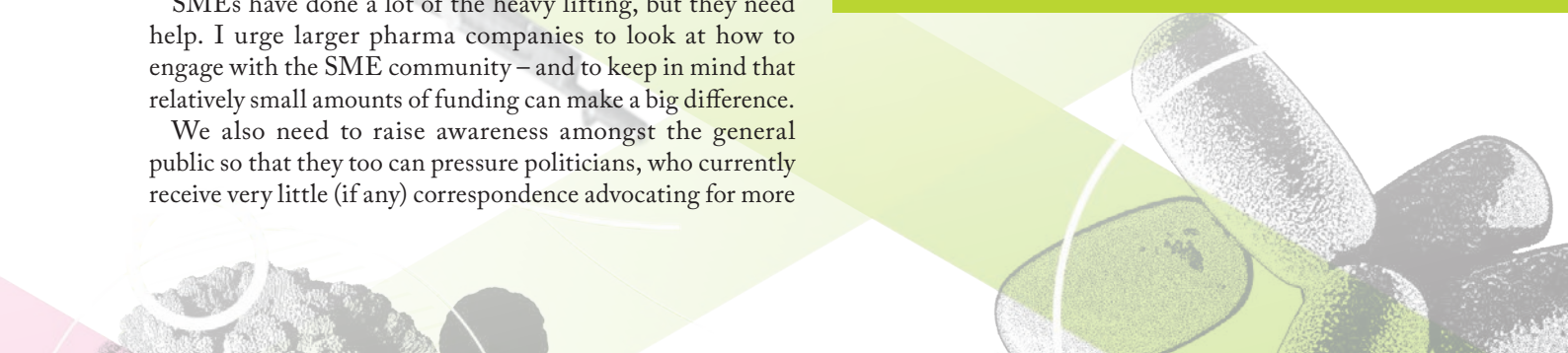
Let's Not Forget About Diagnostics

Other important players in the fight against AMR are good diagnostics. If we can identify the bug and antibiotic sustainability, we can administer the right drug. Simple. However, in many western healthcare systems, these diagnostics are not used – and, even when they are, it can take a day or two to get an answer. If you have a patient in the emergency room with suspected sepsis, you cannot wait – you will hit them with everything you have, which can further exacerbate resistance.



Reduce Waste in Pharma Packaging

What sustainability benefits can be gained by choosing the right blister package material?

By Jared O'Connell, General Manager, Healthcare Packaging, Honeywell Advanced Materials, New Jersey

Patient safety is the top priority for pharmaceutical suppliers when making a packaging selection, but sustainability has become another important consideration. According to the World Economic Forum, adopting innovations that simplify packaging and transportation is one of the top six ways to shrink environmental footprints. (1) This creates a challenge for companies trying to find packaging solutions that meet these needs, but a tool is available to help.

Honeywell's new Aclar® Impact Estimator can help pharmaceutical companies calculate the potential reduction in packaging material, weight, waste, and carbon dioxide emissions by changing their packaging material from cold form foil (CFF) to Aclar ultra-high moisture barrier blister packaging.

The tool was validated and developed using data on Aclar's total cost of ownership, market data, and data provided by customers about the uses of Aclar and CFF. The estimator generates potential reductions based on customizable elements, including capsule size, volume of packages per year, and method of transport. Data can then be used to calculate potential savings, including warehousing and transportation costs, as well as capital expenditures.

The estimator can support the industry's transition to more sustainable practices by demonstrating the tangible impact that waste reduction savings can provide.

(Table 1) By reducing pack size, secondary packaging requirements, and total packaging weight with Aclar, this pharmaceutical company would be able to reduce carbon dioxide emissions equivalent to those produced by driving a car more than 26,937 kilometers (16,738 miles) and save 52 percent of the trees required to make cardboard.

(Table 2) By reducing pack size, secondary packaging requirements, and total packaging weight with Aclar, this pharmaceutical company would be able to reduce carbon dioxide emissions equivalent to those produced by driving a car more than 443,157 kilometers (275,365 miles) and save 47 percent of the trees required to make cardboard.

Aclar is a premium, high-barrier packaging solution designed to protect drugs with high moisture sensitivity. It is the highest moisture barrier polymer available and a more sustainable solution that requires less material to protect the product. Aclar films are used in combination with other polymer substrates, including PET and PP. Its lamination and thermoforming properties allow for a high pill density, reducing pack size and total packaging material used.

Thermoformed Aclar blisters can reduce pack size and secondary packaging by 50 percent on average compared to the same material packaged in CFF (based on the design and dosing regimen). With a higher density of pills per package, suppliers using Aclar can reduce raw material usage, waste, and packaging weight, which can help lower transport-related environmental impact and costs.

Honeywell's Aclar Impact Estimator can support the industry's transition to more sustainable practices by demonstrating the impact waste reduction can provide without sacrificing patient safety or medication efficacy.

To learn more about the Aclar Impact Estimator, visit aclar.calculator.honeywell.com.

Reference

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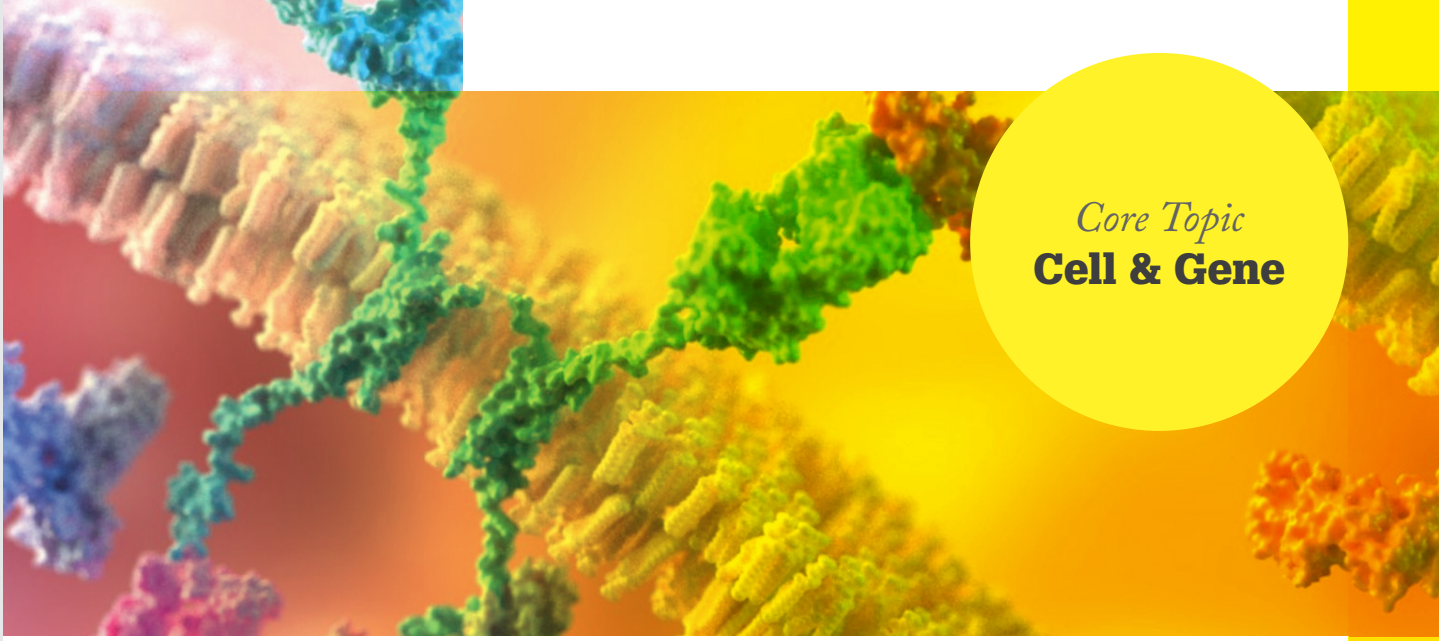
	Barrier blister packaging	Cold form foil	Annual Savings
Total packaging volume (cubic meters)	110	231	122 (53%)
Total packaging weight (tons)	8	14	7 (47%)
Total carbon dioxide emissions (tons)	17	21	4 (18%)
Trees required to produce cardboard	54	112	58 (52%)

Table 1: 1 million packs per year, size 2 capsules, shipped from Houston to Rotterdam, by sea.
Source: https://aclar.calculator.honeywell.com/

	Barrier blister packaging	Cold form foil	Annual Savings
Total packaging volume (cubic meters)	3,299	6,733	3,434 (51%)
Total packaging weight (tons)	236	414	177 (43%)
Total carbon dioxide emissions (tons)	530	592	62 (10%)
Trees required to produce cardboard	1,715	3,225	1,510 (47%)

Table 2: 25 million packs per year, size 0 capsules, shipped from New York City to Chicago, via truck.
Source: https://aclar.calculator.honeywell.com/



Credit: Shutterstock

Core Topic
Cell & Gene

FDA update. The FDA has published draft guidance to assist sponsors of cell and gene therapies on whether certain types of manufacturing changes to their products require the filing of an investigational new drug application or biologics license application. In the document, the agency outlines its current thinking on reporting changes and comparability studies, including how to avoid delays. The guidance states, "To facilitate manufacturing changes during rapid clinical development, CGT product manufacturers should ensure that the pace of product development is aligned with the stage of clinical development. For example, if you initiate clinical studies using product generated by a manufacturing process designed with a potential for scalability, this will help decrease the likelihood of delays later in clinical development when the manufacturing process is scaled up."

Correcting the blood. Researchers at the University of Pennsylvania and Children's Hospital of Philadelphia have developed a proof-of-concept model for using gene editing tools to treat blood disorders (DOI: 10.1038/s41586-023-06300-4). They hope their work will help expand access and reduce the cost of gene therapies for blood disorders, many of which currently require patients to receive chemotherapy and a stem cell transplant. In a statement, the researchers say, "We have shown that it is possible to replace diseased blood cells with corrected ones directly within the body in a 'one-and-done' therapy, eliminating the need for myeloablative conditioning treatments and streamlining the delivery of these potentially life-changing treatments."

CAR T investment. Astellas Pharma has announced a $50-million investment to acquire approximately 8.8 percent of Poseida Therapeutics. Under the current terms, Astellas will receive a right of exclusive negotiation and first refusal for any potential partnering of P-MUC1C-ALLO1 – an allogeneic CAR T cell therapy product candidate for solid tumors. Astellas will also have the right to designate an observer on Poseida's board of directors and scientific board.

Improving Parkinson's treatment. Cell replacement could potentially help in Parkinson's, but the poor survival of grafted neurons is a problem. Scientists from Harvard Medical School have shown that co-transplanting stem cells with regulatory T-cells – immune cells that dampen excessive inflammatory responses – can boost cell survival in the brain in rodent models and ease motor symptoms (DOI: 10.1038/s41586-023-06300-4). These findings propose a new strategy to achieve better clinical outcomes for stem cell-based therapies for Parkinson's in humans. Such therapies aim to replace the dopamine-producing nerve cells that are lost in people with the neurodegenerative disorder.

IN OTHER NEWS

Mustang Bio amends previous cell and gene manufacturing partnership with uBriGene Biosciences to enhance cash position.

Abeona Therapeutics submits briefing package for pre-biologics license application meeting with FDA for EB-101 cell therapy for recessive dystrophic epidermolysis bullosa.

FDA grants fast track designation for Genprex's lead gene therapy candidate Reqorsa for patients with extensive-stage small cell lung cancer.

SCG Cell Therapy opens manufacturing facility and R&D center in Singapore to reduce cost and increase local production of cell therapies.

FDA says it will not schedule an advisory committee meeting for bluebird bio's lovo-cel gene therapy for sickle cell disease.

Top Cell & Gene Prospects

Experts discuss the most exciting cell and gene trends – and make bold predictions for the future

What are the biggest prospects for cell and gene therapy – and what excites you the most?

Matthias Bozza (Vector Biopharma): The possibility of reverting genetic errors using nuclease-free systems, such as base or epigenetic editors, is of great interest because of their high safety profile. These editors possess the unique ability to precisely and reliably elicit single base edits in the genome; genetic disorders that can be cured by fixing one nucleic acid will be the ones that benefit the most.

Michelle Fraser (Revvity): As the field progresses, we are starting to see a shift from autologous cell therapies to allogeneic cell therapies, which offer the benefits of scaled up manufacturing, off the shelf therapies, and reduced costs. There is also a move from academic research and product development towards industry taking the lead. The benefit of having industry engagement is that they bring the systems and processes to develop, manufacture and deliver cell and gene therapies globally.

I am also excited by newer generation editing systems, such as base editing, that offer more controlled gene editing. The development editing systems also underpins the groundswell of innovation around alternate Cas enzymes, including i) different effector molecules that can be deployed alongside cytosine and adenosine base editors, ii) the ability to multiplex gene knockouts in a single reaction to make therapies more efficient, and iii) the potential to simultaneously knock-in genes, such as a CAR, to create a CAR T therapy to treat cancer.

Stacy Treichler (Catalent): High levels of investment in the field have led to an increase in the number of novel cell types and proprietary technologies entering the clinic. Autologous therapies are currently the most numerous, but there is a trend towards a greater number of clinical trials being initiated for allogeneic therapies. It is all very exciting, but companies need to find a way to make these breakthrough therapies affordable to all.

Chelsea Pratt (Bio-Rad): The introduction of in vivo gene editing techniques, such as CRISPR-Cas9, has propelled the field forward, providing exceptional precision in addressing rare genetic conditions. We've also seen the approval of a new type of therapy with Sarepta Therapeutics' SRP-9001 gene therapy for Duchenne muscular dystrophy (DMD), a genetic neuromuscular disease that affects 1 in 3,500 to 5,000 males born worldwide.

However, a significant hurdle faced by these treatments is the limited number of patients available for clinical trials in a given rare disease. Recognizing this challenge, different regulatory agencies are engaged in collaborative discussions to harmonize clinical trial requirements.

Angela Osborne (eXmoor Pharma): Since I started in this field, people have said things like "autologous therapies aren't going to last; allogeneic is the future," or "viral vectors won't last; our focus will shift towards non-viral deliveries." I believe there is a space for everything – but it will be indication dependent.

The biggest opportunity in the field is moving towards the mass market. Moving from monogenetic diseases and orphan drugs, to major diseases, such as Parkinson's disease, liver disease, heart disease, will become our collective focus. Solving these issues will be dependent on robust processes – whether it's a scale out or scale up, it's about getting your development focus right.

Phil Vanek (Gamma Bioscience): There is a growing focus towards pluripotent stem cells and their ability to drive allogeneic therapies, while continuing to solve the cost of manufacturing for autologous therapies. As an industry, there is room for both autologous and allogeneic therapies for different indications and for different acuteness of therapy. I can foresee the evolution of technologies to be better suited towards the indications of what the industry needs right now. Certainly, with gene therapy, the argument is whether we can ever get beyond the virus gene delivery platform, and look at direct LNP delivery into cells in a targeted fashion – these are areas for rich discussion over the coming weeks, months, and years.

THE EXPERTS

Matthias Bozza – Director of Gene Regulation at Vector Biopharma
Michelle Fraser – Head of Cell and Gene Therapy at Revvity
Stacey Treichler – Director, Head of Marketing & Strategy of BioModalities at Catalent
Chelsea Pratt – Biopharma Segment Marketing Manager at Bio-Rad Laboratories
Angela Osborne – CEO and Founder at eXmoor Pharma
Vered Caplan – CEO at Orgenesis
Phil Vanek – CTO at Gamma Bioscience

Care to make a bold prediction about the future of cell and gene therapies?

Vered Caplan (Orgenesis): When people ask me about cell and gene therapy, I can't help but say, "You don't know what is coming!" We are literally learning how to reprogram advanced cellular function, and I couldn't be more excited. To enable growth in this industry, we need to standardize and converge. We don't have to invent the wheel per say; perhaps there are basics we can adapt from other industries.

I'm particularly interested in the development of autologous therapies. The moment we pull together our knowledge on how to effectively use these processes, is the moment we will take off as an industry.

Fraser: In the not too distant future, I can imagine patients having their DNA screened for genetic errors that are known to be linked to disease before their symptoms are evident, and then an allogeneic therapy will be administered as a preventative medicine. Functional genomic screening is already providing insight into the pathways within a cell that are causative of disease symptoms, so we're getting better at finding the link between mutation and disease. Many diseases are multifaceted, so having a defined set of mutations that can lead to a diagnosis, then being able to select the right cell or gene therapy that matches the cause, will launch the future of truly personalized and affordable medicine.

Treichler: In the immediate future, I think we need to focus on the transient transfection step to increase the efficiency of gene therapy manufacturing. The ultimate goal would be to generate stable producer cell lines in the process that do not undergo this step before every manufacturing batch. However, there remain challenges to generate cell lines that can stably express the pHelper, rep/cap, and gene of interest with high titers and capsid fill rates. Though a stable cell line might be the solution, the next step to allow more efficient transient transfection (and a pathway to stable AAV production cell lines) could be to integrate the rep/cap and Helper into a single plasmid, so that fewer plasmids need to be made and banked per therapy.

Pratt: Within my lifetime, I believe we will see widespread adoption of in vivo treatments for diseases such as hypercholesterolaemia and type I diabetes. Hypercholesterolaemia and diabetes affect millions of people globally, posing significant health risks and straining public healthcare systems. Cell and gene therapies hold the potential to revolutionize the long-term management of these conditions, or potentially offer cures.

the Medicine Maker

INNOVATION *Awards*

NOMINATIONS ARE OPEN *for The Innovation Awards 2023!*

Vendors and users are invited to nominate the best drug development and manufacturing technologies to be commercially released during 2023

Scan the QR code to submit your nomination - https://bit.ly/444s7lC

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Core Topic
Bioprocessing

Single use and sustainability. Academics from University College Cork, Ireland, have evaluated the impact of buffer management and technology selection on overall process efficiency by examining process mass intensity (DOI: 10.3390/pr11082242). The result? Buffer management can have a huge impact – in some cases reducing process mass intensity by 90 percent. The authors also concluded that single-use systems are superior to stainless steel when it comes to overall process efficiency. However, process mass intensity is an indirect measurement of environmental performance. The authors write, "Further research is currently underway into the direct environmental impact of buffer management philosophy, which would be of great benefit to further validate the correlation between PMI and environmental performance, particularly because research related directly to buffer management is limited."

Major mAb breakthrough. One of the biggest talking points in biopharma recently is the FDA granting traditional approval for Leqembi (lecanemab) for Alzheimer's disease, after the drug met all primary and key secondary endpoints in a phase III trial. In addition, Eli Lilly has published results from a phase III trial of its own Alzheimer's mAb candidate: donanemab. The results appear to show that the drug can slow decline by as much as 60 percent, with the biggest improvements seen in those at the earliest stages of the disease. Both drugs help to remove beta amyloid from the brain.

Sandoz in Slovenia. Earlier this year, Sandoz announced plans for a new biologics manufacturing plant in Lendava, Slovenia, and an expansion of its Holzkirchen facility in Germany (an investment of at least $400 million). Now, it is further bolstering investment in Slovenia with an additional $90 million to establish the Sandoz Biopharma Development Center (by 2026) at its Ljubljana site. In a statement, Sandoz explained that the site would become a key location for biosimilar product development at the company. Around 200 new jobs will be created as a result of the new expansion.

Battle of the giants. GSK has filed a patent infringement lawsuit against Pfizer for its RSV vaccine Arexvy. GSK alleges that Pfizer's own RSV vaccine Abrysvo infringes four of GSK's patents involving RSV antigens and RSF F protein compositions. The filing states, "Upon information and belief, Pfizer began the project that led to Abrysvo no earlier than 2013, at least seven years after GSK started its RSV program." GSK is seeking monetary damages and wants to block Abrysvo from being sold or imported into the US for adults over the age of 60. GSK is not seeking to restrain use of Abrysvo in pregnant individuals to prevent disease in infants.

IN OTHER NEWS

The Bio-Process Systems Alliance has released part two of guide on X-ray sterilization of single use bioprocessing equipment, focusing on qualification data.

Lonza launches TheraPRO CHO cell culture platform to optimize productivity when used with GS-CHO cell lines.

Eli Lilly to acquire Versanis; lead candidate bimagrumab is undergoing a phase IIb study for cardiometabolic disease in obese adults.

Emergent BioSolutions wins 10-year contract from BARDA for development, manufacturing, and procurement of Ebola vaccine Ebanga.

Merck/MilliporeSigma invests $25 million in Kansas facility to expand lab space by 9,100 square meters and enhance production of dry powder cell culture media.

The Future of Biopharma Analytics

Smarter, simpler mass spectrometry, on-line PAT, and multivariate data analytical tools – what lies ahead for biopharma manufacturers when it comes to downstream analytical tech?

Featuring Magnus Wetterhall, Global Marketing Manager – Bioprocessing, Waters Corporation

What type of analytical data is important for downstream manufacturing of biopharmaceuticals?

Downstream manufacturing is all about purifying the drug substance molecule into a final drug product that is effective and safe to administer to patients. Analytical tools that provide information on the purification process to remove both process related impurities (buffer and host cell components, leachables, and so on) and product-related impurities (for example, aggregates and fragments, misfolded and mistranslated product, wrongly modified variants of the products) to the acceptance levels of the filed and approved process/product are essential. Tools and data are also needed to follow the drug substance throughout the purification process – not only to ensure that the product is present after each purification step, but also to adjust input levels, such as load volumes and times, into the next step. Finally, of course, the end-product – the drug substance itself – must be analyzed before it can be approved for release to patients.

What are the biggest analytical advances of the last decade?

Well, because I am an analytical chemist by training and a passionate mass spectrometrist, I would say that the adoption of comprehensive analytical tools, such as liquid chromatography (LC) and mass spectrometry (MS), into process development and manufacturing is a significant milestone. Of course, the implementation of new and better performing in-line analytics, such as multi-angle light scattering and Raman spectroscopy are also fundamental milestones. Finally, I would also mention the implementation of multivariate data analytics and quality-by design (QbD) approaches to be important advances.

What are today's most powerful analytical tools and approaches?

Perhaps I am biased, but this question only has one answer for me: mass spectrometry is both extremely selective and universal when it comes to applications and measuring molecules. It is sensitive, accurate, and gives both quantitative and high-resolution structural information in one and the same analysis. It can also be readily combined with various separation techniques that provide further information of the critical product and process parameters needed. All of these are fantastic features of mass spectrometry, but the one thing that tips the scale for me is that MS directly measures the target molecules of interest. Nothing can beat that. Many other technologies are indirect and, therefore, not as specific.

Although I am a dedicated MS fan, there are some drawbacks and limitations when applying MS in bioprocessing. First, it is not an in-line process analytical technology (PAT). It is still today often applied at-line or off-line (although great efforts are being made to implement MS as an on-line PAT for bioprocessing). Traditionally, many people think of MS as complicated and for highly-skilled operators. That perception is currently shifting with more automated and easy-to-use instrumentation that is designed to be fit for purpose.

Another limiting factor of MS is that it is a rather expensive technology – but this too is changing as more fit-for-purpose and simpler instrumentation is commercialized.

Are there any other barriers to wider adoption of MS or LC-MS-based PAT?

The understanding, acceptance, and maturity of the industry to adopt MS into their processes is a barrier, but this is beginning to change. Here, I want to highlight the work and effort of regulators, such as the FDA and EMA, to encourage and drive the industry to adopt MS and LC-MS. The reason for the regulatory interest is twofold: first, PAT delivers more and better information for developing newer, more robust manufacturing processes. Second, it makes it possible to release safer treatments to patients faster.

The end benefits of MS and LC-MS-based PAT far outweigh any existing barriers to the adoption of these techniques. At Waters, it is our task, as technology providers, to innovate and develop automated, easy-to-use, robust, high performing, and affordable MS solutions to lower those barriers of adoption even further.

As the industry moves to continuous manufacturing for biologics, how do analytical needs change?

Continuous manufacturing of biologics means that there are now hold up times or intermittent downstream purification steps in the process, implying that deployed PAT should provide continuous data. Thus, real time monitoring is a requirement for continuous manufacturing. Real time monitoring is only possible with in-line and on-line PAT solutions. The industry is not at this point yet. We have seen proof of concept for continuous

"We are moving towards more comprehensive in-line and on-line PAT."

manufacturing, but the solutions are still not mature enough for large scale manufacturing adoption.

We will get there; it is just a matter of time!

What other significant challenges do biopharma manufacturers face when it comes to analytics?

One challenge I want to highlight is the shortage of skilled personnel. For me, it is worrying, and it makes me sad that the natural sciences, such as chemistry and biotechnology, are not as popular as in the past. The demand is great, and bioprocess and biologics manufacturing have grown almost exponentially over the last few decades, but it is still difficult to find skilled and properly trained personnel. Some of that can be addressed with automation and analytics, but they will not, and should not, replace having skilled personnel at your manufacturing facilities.

Other important challenges for manufacturers are security of supply, sustainability, and reducing pharmaceutical development and manufacturing times and costs. It can seem a bit paradoxical, but I am convinced that making the investment in more comprehensive and expensive PAT technology will, in the end, save both time and money. Multi-attribute-based PAT will provide greater manufacturing insights and facilitate faster process development, driving higher manufacturing efficiency. This, in turn, will reduce the risk of batch failures.

And what about analyzing data? What potential is there here for further advances?

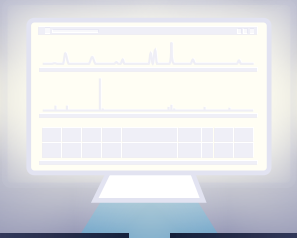
The potential for further advancing data analytics is massive. We need to implement multivariate data analytical (MVDA) tools to process and get the best outcome from multiplex and comprehensive LC-MS. Being able to use MVDA tools to correlate process inputs with product outputs will greatly enhance the development and manufacturing of biologics and pharmaceuticals. Other data analytical tools for design-of-experiments have proven to be extremely valuable for more efficient process development. One major driver is to combine the advanced PAT and data analytic tools in integrated and automated platforms that are straightforward to use for non-experts.

What does the future of analytics look like?

We're just starting to explore a vast ocean of possibilities in which agility, continuous operation, real-time monitoring, and digitalization will play important roles. This will necessitate the increased use of robust and reliable high performing in-line PAT and on-line solutions.

I can't predict the future – but the trends are pretty clear. We are moving towards more comprehensive in-line and on-line PAT that will enable real-time monitoring and release. MS and LC-MS based solutions will play a vital part in these developments. We will also see plug-and-play automated solutions for on-line aseptic sampling, sample processing, and analysis at point of need. There is a need for fit-for-purpose PAT that is easily integrated into control system software platforms to achieve true real time process control. All of these technologies, solutions, and workflows must be easy to use in the hands of operators and compliant and compatible for the regulated manufacturing setting.

One Software Interface for All Your Analytical Data



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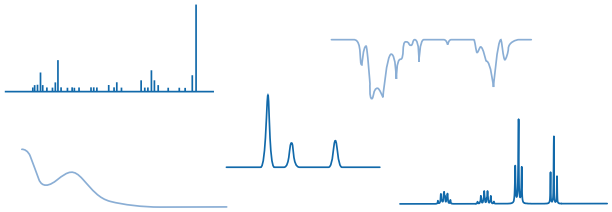

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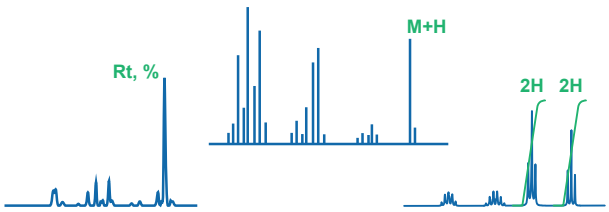
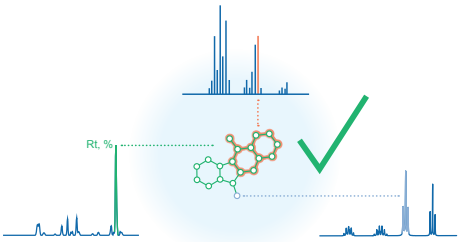


Structure Integration



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Core Topic

Small Molecule Manufacture

Hypertension potential. Roche has agreed a partnership with Alnylam to develop and commercialize zilebesiran, an investigational RNAi therapeutic currently in phase II for the treatment of hypertension. According to the companies, zilebesiran could be "potentially transformative" for reducing morbidity and mortality in patients with hypertension. The drug also has the potential of improved patient adherence because of the possible biannual subcutaneous dosing regime.

Studying statins. An NIH-supported study has found that cholesterol-lowering statins could offset the risk of cardiovascular disease in people living with HIV by more than a third. People living with HIV are at a 50-100 percent increased risk of cardiovascular disease. Published in NEJM, the research suggests that "statins may provide an accessible, cost-effective measure to improve the cardiovascular health and quality of life for people living with HIV," according to NHLBI Director Gary H. Gibbons, who co-funded the study. "Additional research can further expand on this effect, while providing a roadmap to rapidly translate research findings into clinical practice." (Steven K. Grinspoon, et al, "Pitavastatin to Prevent Cardiovascular Disease in HIV Infection", NEJM, DOI: 10.1056/NEJMoa2304146)

Fleming legacy. To mark a century since the discovery of penicillin, Imperial College Healthcare NHS Trust and Imperial College London in the UK have launched an appeal to build The Fleming Centre, with the goal of inspiring new solutions to tackle global antimicrobial resistance (AMR). The centre will open in 2028 and will be based at St Mary's Hospital, London, where discoverer Alexander Fleming's laboratory remains. Chaired by Lord Darzi of Denham, the center will aim to drive solutions to AMR alongside patients, the public, and policy makers. In a statement, Darzi said, "We are making behavioral science and public involvement the cornerstones of the radical change that's needed to influence individual behavior and policy decisions."

Support for science. Medicxi has announced its $400 million Medicxi IV fund to support drug developers. Medicxi's investments have resulted in the development of several marketed and late-stage development drugs, including Alunbrig, Voquezna, and obicetripib, as well as biopharma products. Francesco De Rubertis, Co-founder and Partner at Medicxi, said, "Our mission is to support the innovative genius of entrepreneurs by providing the critical capital, expertise, and experience that form the all-important bridge to pharma. This new fund consolidates Medicxi's position as a key operating platform for scientific entrepreneurs and drug hunters and is deliberately sized for our investment model."

IN OTHER NEWS

Axplora installs new cGMP pilot unit in Leverkusen, Germany, continuing its investment in differentiating and specialized technologies.

Delhi's Department of Drugs Control restricts the sale of over the counter painkillers without prescription because of a rise in vector-borne diseases dengue and chikungunya.

Kilmarnock Football Club unveils penicillin-inspired kit; renowned scientist Sir Alexander Fleming studied in the Scottish town.

Novartis's Vas Narasimhan warns US drug pricing reform risks public health as drugmakers cut investment in geriatric medicines.

UK government recalls some Quantum Pharmaceutical Diltiazem batches with reduced viscosity where the product more closely resembles a lotion than a cream.

Blisters of Mercy

Child exposure to pharmaceutical substances appears to be decreasing, but what more can packaging companies do to push the trend?

US-based Keystone Folding Box serves the packaging needs of pharmaceutical and healthcare manufacturers from the busy port of Newark, New Jersey. Having grown up in a family of pharmacists, Director of Marketing and Business Development Ward Smith shares the same passion for innovation and service as those involved directly with the medicine making process. Both his father and grandfather owned and operated independent pharmacies, where Smith worked from a young age before earning a degree in communication studies at Florida State University. From there, Smith was recruited into the packaging industry, where – due to a series of positions with escalating responsibility and more than 3,000 packaging projects – he has found a way to continue the legacy set down by his pharmacist grandfather.

"I can safely say that every product's packaging requirements are unique," Smith says. "At the same time, there are certainly similarities that could be adopted, transferred, or modified in some way."

Here, Smith shares how pharma packaging specialists are a vital part of the supply chain and how his own problem solving skills help improve product quality and patient outcomes.

What do you find most rewarding about packaging for the pharma industry?

Our large pharmaceutical client base is always challenging us to create unique packaging solutions, but one of my most satisfying professional experiences has been the award of a co-patent for a reclosable, eco-friendly, child-resistant paperboard pack for blister packaged products. Over 250 million of these are now in use by a leading national pharmacy retailer. Developing packaging innovations that have real-world application is a key part of what we do. An idea must "hit on all cylinders" to become a commercial reality. Unless a package enhances patient health and makes sense operationally, economically, and sustainably, it's little more than just a neat idea.

What are the important standards when it comes to child-resistant packaging?

The standards have not really changed in recent years, but it is important to make the distinction between what is child-proof and what is child-resistant. When designing packaging for pharmaceutical products, we follow the guidelines outlined in the Poison Prevention Packaging Act 1970, as well asthe related regulations (codified at: 16 CFR Subchapter E (parts 1700 to 1702)).

Child-resistant or "special packaging" is designed or constructed to be significantly difficult for small children to open or for them to obtain a toxic or harmful amount of the substance, but not difficult for adults to use. Child-proof packaging cannot be opened by small children at all.

Has there been a distinct and quantifiable reduction in child harm since the introduction of safety packaging?

A report published in 2021 conducted a retrospective analysis of the 2009 to 2019 National Poison Data System (NPDS) annual reports to examine trends in US poison exposures and related fatalities in children. The findings signal an overall linear decreasing trend in childhood poison exposure to pharmaceutical products. During the study period, children in age groups of 0–5 and 6–12 years experienced an overall decrease in poison exposures. In summary, from 2009 to 2019, the annual number of reported poison exposures in US children decreased significantly.

Looking at the increase in use of child-resistant blister packages, we believe the rate of reduction is due, in part, to a growing use of blister packages. Consider that when caps are inadvertently left partially closed or off the bottles, the child-resistant feature becomes irrelevant. In contrast, blister packs can provide a significantly higher level of safety for children. Some blister solutions can provide a child-resistant safety level of F=1 – the highest child-resistance rating available.

Can you explain exactly how blister packs improve safety?

If a child is able to remove a bottle cap, the child has access to all the contents in a single moment. Blister packs require extra effort and time to remove each pill, significantly slowing down the child's access. By adding a child-resistant feature to the blister package, children have an even lower chance of accessing a single dose, much less multiple doses.

Do government agencies need to improve existing safety standards?

Tragically, there has been an increase in deaths of children who are exposed to poisoning by opioids. To help combat the ongoing opioid epidemic in the US, the FDA and the Institute for Safe Medication Practices are encouraging changes to product packaging that help to deter abuse. This specifically includes promoting the use of limited doses dispensed in blister packs.

In 2018, a bill, known as the SUPPORT Act, was passed into law that allows the FDA to require special packaging for such drugs, including customizable fixed-quantity blister packaging for opioids and other drugs that pose a risk of abuse or overdose. The

FDA is currently seeking feedback on potential use of this new authority to require that certain immediate-release opioid analgesics be made available in fixed-quantity, unit-of-use blister packaging. To date, the FDA has not issued guidance, nor has it in any way forced drug manufacturers to adhere to required packaging changes.

Ward Smith, Keystone Folding Box

Are child-resistant caps/closures or blister packs safer?

In terms of safety, studies have consistently shown that blister packaging outperforms child-resistant bottles. In a March 2018 broadcast, CBS News reported on a study citing "Blisters are 65 percent more effective in preventing child access to medication." The report further states that kids can open child-resistant pill bottles in seconds, risking accidental poisoning. In a test that the group set up at a Maryland day care center, children aged 3–5 managed to pop open child-resistant pill bottles in mere seconds.

How is Keystone factoring in wider trends such as sustainability and the circular economy?

Plastic aside, another issue with all bottles is that size does indeed matter. According to the Association of Plastic Recyclers (APR), "Items smaller than two inches in two dimensions render the package non-recyclable […] The industry standard screen size loses materials less than two inches to a non-plastics stream […] or directly to [landfill] waste." In other words, amber vials' small size is why US landfills are filling up with tiny amber containers – with prescription labels still attached. This applies to high-density polyethylene (HDPE) bottles too.

But blister packages aren't recyclable either, right? The materials used to form the blister are typically PVC- or aluminium-based, which render the product non-recyclable. Historically, that has indeed been the case because the amount of plastic in a blister package is exponentially less than that in an amber vial. So, if we assume the likelihood that neither will be recycled, blister packages are less environmentally damaging because they beat bottles on one of sustainability's three Rs: "reduce." In some cases, a switch from bottles to blisters can reduce the amount of plastic going to landfill by 80 percent. Fewer plastics equals more eco-friendliness – an equation that has been accepted as true for decades.

Recently, an additional factor – the introduction of recyclable blister materials made from HDPE – has shifted the math even further toward blister packs. HDPE presents incredible potential for drug manufactures and large retail pharmacies to further reduce plastic landfill waste. Several prominent films suppliers have shown both the barrier viability and comprehensive recyclability of these next-generation films to produce blister packaging. This seems revolutionarily right now, but in five years it will be commonplace.

Thus far, however, recyclable blister constructions alone have faced a crucial challenge: child-resistance. Simply put, it's difficult to make a blister with a high-level feature both effective and recyclable. It's a materials science hurdle that hasn't yet been solved.

However, by pairing a recyclable blister with a secondary paperboard carton with F=1 child-resistance, a truly sustainable medication package can improve the way we deliver both OTC and prescription drugs to the market. When finished with the package, the consumer simply separates the paperboard card from the blister component and recycles each.

NextGen

R&D pipeline
New technology
Future trends

Getting Results Through Novel Solubility-Enhancing Excipients

Every innovation begins as an idea, but it takes partnerships to bring them to life

Featuring Joey Glassco, Senior Global Marketing Manager at LLS Health

The Apisolex polymer from Lubrizol Life Science Health (LLS Health) was the winner of The Medicine Maker 2022 Innovation Awards. An injectable-grade excipient that can help enhance the solubility of BCS class II and IV APIs by up to 50,000-fold. Apisolex excipient is designed to work with simple formulation techniques that streamline manufacturing and minimize API loss. The resulting formulation is stable and can be readily resuspended in common diluents for administration. In saline, the lyophilized drug product reconstitutes in less than 30 seconds.

We spoke with an "honoured" Joey Glassco from LLS Health about what makes the Apisolex polymer so innovative, and how she hopes it could help accelerate life-saving drugs to market.

What is your background? And what about LLS Health?

I've been with Lubrizol for 27 years this year. That sounds ridiculous, right? Nobody stays with a company for 27 years anymore, but that's the truth! I've been in various strategic marketing and new business development roles for 24 years, and on the pharma side of the business for over 10 years now. I have excipient and formulation experience with oral, implantable, and injectable drug products, and look forward to what we do next in the injectables space.

In 2015, Lubrizol acquired Particle Sciences, which manufactured complex injectables and subcutaneous devices, among other things. Prior to the acquisition, they were using our polymers in devices and were skilled at increasing the solubility and bioavailability of actives. In fact, I would describe Particle Sciences as world experts in nano milling, which is a method of increasing the solubility of actives. In 2019, Particle Sciences was rebranded to LLS Health.

Why are (novel) excipients so important?

Excipients are important because you can have the greatest API in the world, but if you don't have an effective delivery system to get it into the body that is bioavailable, it doesn't have much use. The low-hanging fruit in terms of water-soluble APIs is already marketed, so excipients are needed to boost the solubility and bioavailability of newer drugs coming through pipelines (most of which have significant solubility issues).

The last injectable excipient, a modified cyclodextrin, was introduced into the market over 20 years ago. It's a great

product for many APIs, but, as part of my job, I'm talking to people all day and there are many out there who have yet to find a solution to their API solubility issues. Novel excipients can be the solution to otherwise unsolved formulation issues and could help bring more new chemical entities to market. There are also amazing molecules already on the market that are suboptimal because of a lack of excipient options. These products could be improved using the 505(b)(2) regulatory pathway, wherein the API has an opportunity to be repurposed for another indication or a different route of administration, for example.

How does the Apisolex polymer work?

The Apisolex excipient is an encapsulating, amphiphilic multi-block copolymer that incorporates a hydrophilic polysarcosine block and a hydrophobic DL-mixed polyamino acid block. Polymers of sarcosine offer an inert replacement to traditional solubility-enhancing polymers such as PEG and PVA. Apisolex excipient substantially increases the achievable concentration of API and water – with up to 40:100 API to solubilizer ratio; contrast that with other complexing agents that may hit only 1:100. Put another way, Apisolex polymer can increase the solubility of

an API by as much as 50,000-fold, providing a stable lyophilized drug product or solution-based product if the API itself is stable. Apisolex polymer also uses standard, straightforward, and scalable techniques, which can be used for feasibility studies all the way up through commercial manufacturing.

There is an outstanding need for more solubility solutions in drug development and I firmly believe that Apisolex excipient can help drug formulators achieve their drug delivery goal in areas such as oncology, CNS, and anti-infectives. I really hope that we can play a part in improving outcomes for patients.

What was the inspiration for development?

Historically, Lubrizol has been an ingredient supplier and we noticed that conversations between drug product companies and their excipient suppliers tend to be quite guarded. Because we wanted to focus on growing in the injectable, pharmaceutical, and biopharmaceutical spaces, we acquired and became a CDMO. This move also allowed us to have frank and open conversations about market trends, unmet needs, and potential solutions.

As a CDMO, inventors often approach us with new technologies (which we love, by the way). If the technology has valid IP and a good value proposition, we take a closer look. This is exactly what we did with Apisolex excipient; the inventors brought the technology to LLS Health. We tested it, we saw the value, we licensed it, and we introduced it to the market. We've also used our existing chemistry in acrylic acid-based polymers to invent a new polymer called Apinovex excipient for the solubility enhancement of oral products. Ultimately, we want our company to be seen as a solution provider for solubility issues with either our CDMO services or solubility enhancing excipients.

The launch of the Apisolex polymer is a great collaboration between the excipient and CDMO sides of our business. Our years of experience in selling and marketing excipients helped with streamlining the manufacturing and regulatory components of the polymer for market.

We took an idea and commercialized it, and we want to do more of this. The original inventors had a great product but just needed a little extra excipient expertise to move it forward. That's the power of partnership and collaboration.

What were the biggest challenges during development?

The most difficult part of commercialization has been the bench to commercial excipient process. When we licensed the polymer, we knew that the residual solvent levels were not where we wanted them to be, so in lieu of jumping right into the market with a suboptimal excipient, we updated the manufacturing process and repeated all the GMP work to get the right product in place. It has not been inexpensive, and it's taken longer than we wanted due to COVID-19-related delays.

More broadly, what are the challenges that manufacturers face in developing novel excipients?

The biggest challenge for excipient manufacturers is always market acceptance. Even though two new chemical entity (NCE) products were approved in 2002, it took over 10 years for the Captisol (modified cyclodextrin) excipient to take off in the market – and that was only after the company launched its own 505(b)(2) products.

"All novel excipient developers are also eagerly awaiting the outcome of the FDA pilot program."

Drug product manufacturers need to be willing to experiment with novel polymers, while excipient manufacturers need to be willing to provide safety data and compelling case studies to justify the research. There needs to be an API with the right patient value proposition to make it work for all parties. Unless IP is the play, rarely is anyone going to use a novel excipient if a different off-the-shelf polymer works instead.

Excipient manufacturers are investing millions of dollars to bring these excipients to market, with absolutely no guarantee that anybody is going to use them. This is a big market risk, but we believe that these new excipients can deliver better drug products for patients.

If drug developers aren't willing to use novel excipients, we'll be sitting here 10 or 20 years from now with exactly the same solubility challenges in formulation. I'm not saying that the industry absolutely must try novel excipients, but if folks want things to change, it has to start somewhere.

What new initiatives could help solve these challenges?

To help solve the market acceptance issues, we are advancing some solubility feasibility programs. These would be short, fee-for-service programs where we take an API and very quickly run a feasibility screening with either Apisolex or Apinovex excipient at our CDMO in Bethlehem, Pennsylvania. We're hoping to use that program to encourage drug developers to try new excipients to learn whether or not the polymer works with their particular API.

All novel excipient developers are also eagerly awaiting the outcome of the FDA pilot program created in 2021 to foster the development of new excipients, but this alone will not do the trick. The FDA's pilot Program for the Review of Innovation and Modernization of Excipients (PRIME) is great, but it requires a lot of data to have your submission selected for review.

Every API is different, and what works for one will not work for another. Even with novel excipients, there will always be technical challenges for formulators. We have data comparing what Apisolex excipient can do versus other excipients, and there are other great excipients on the market that are very useful, but they're not useful in every case.

Finally, how do you feel about The Medicine Maker Innovation Awards?

The Medicine Maker Innovation Awards are a great way to bring awareness to important new technology that, in our case, can help bring important medications to market. That's the real value in it. I'd like to say thank you to all the readers who voted for our technology. You have increased awareness of a novel technology that might have the ability to change someone's life.

The 'Tides are Turning

Here's why oligonucleotides are such a promising new modality in therapeutics

Featuring Nigel Richardson, Director of New Modalities at CatSci

After more than 20 years of experience in chemistry, Director of New Modalities at CatSci Nigel Richardson has led numerous projects, including chemical route selection, clinical supply and control strategy development, regulatory submission generation, and technology transfer. He is also the founder of McLean Pharma Consulting, where his mission is to help companies accelerate the development and delivery of new therapies to waiting patient populations.

His interest in oligonucleotides began when he realized their potential to help treat Duchenne Muscular Dystrophy. Looking back to one project, Richardson says, "The mechanism of action was unlike any small molecule medicine I had worked on before, and the elegance of RNA interference to enable the production of a dystrophin-like protein as a potential cure for Duchenne is a fascinating area of scientific innovation with huge impact on the waiting patients."

Richardson has since gone on to develop the necessary chemistry and analytical controls to ensure high-quality oligonucleotide medicines can be manufactured at a commercial scale in support of product registration. With the manufacture and characterization of oligonucleotide therapies being so extremely complex, we asked Richardson why they are so important – and what is likely to come next in their ongoing development.

Why is it so important for the pharma industry to invest in oligonucleotide research?

Oligonucleotides can be considered the third modality of therapeutics, building on traditional small molecule drugs and biopharmaceuticals. The most common oligonucleotide therapeutic agents include antisense oligonucleotides (ASOs), small interfering RNA (siRNAs), micro-RNA (mRNA), and aptamers. Oligonucleotide therapeutics are all based on short sequences of chemically modified or unmodified nucleic acids. The mechanism of action varies depending on the type of oligonucleotide, but the common factor for all types (except aptamers) relies on Watson-Crick base pairing to the target messenger RNA. The importance of oligonucleotide therapies is based on the unique ability of RNA interference to silence or, in some cases, enable protein production. This mechanism of action has the potential to develop medicines for formally undruggable diseases.

With the increased understanding of the human genome and the genetic link to many diseases, the drug discovery process for oligonucleotides (the design of a short oligonucleotide sequence to interfere with a specific messenger RNA) is accessible to many small biotechnology organizations and academic groups. This activity is accelerating innovation in the field, as well as increasing the number of clinical trials.

In what therapeutic areas are oligonucleotides making their mark?

Depending on the definition used, around 14 oligonucleotide medicines have been approved across all marketing authorisation. A number of the approved medicines are ASOs for the treatment of Duchenne Muscular Dystrophy – and employ slicing modulation (exon skipping) mechanism for each specific mutation. Many of the other approved medicines target liver diseases. Perhaps the most significant of these is Inclisiran, marketed as Leqvio – an siRNA that silences the transcription of the protein PCSK9 to help reduce cholesterol in the blood. The drug represents a new treatment for people with high cholesterol that cannot be reduced by more conventional treatments and is the first oligonucleotide therapy for large patient populations.

The application of oligonucleotide therapeutics in oncology is a large and developing field with a significant number of ongoing clinical trials. There is also a focus on ASOs for neurodegenerative diseases. Delivery to the brain was demonstrated with the approval of Nusinersen, marketed in the US as Spinraza, for the treatment of spinal muscular atrophy (SMA) in 2016.

What other approvals in the field can be considered milestones?

The oligonucleotide therapies that have been approved over the last five years have demonstrated significant advances in the general technology platform. In 2016, patisiran, marketed as Onpattro, was the first siRNA to be approved. Onpattro, for the treatment of TTR amyloidosis, uses lipid nanoparticle technology to deliver the siRNA to the liver. This milestone achievement signaled the beginning of further siRNA therapeutics. In 2019, givosiran, marketed as Givlaari, was approved for acute hepatic porphyrias.

"The application of oligonucleotide therapeutics in oncology is a large and developing field."

Nigel Richardson of CatSci

Givosiran incorporates a GalNAc conjugate, a carbohydrate that binds to the highly liver expressed asialoglycoprotein receptor 1 (ASPGR) with high affinity, to target the liver. This approval marked the beginning of a further wave of oligonucleotide medicines that incorporate GalNAc. The approval of Inclisiran – an siRNA containing the GalNAc moiety – is the first oligonucleotide treatment for a large patient population.

What are the manufacturing challenges?

With the progression of oligonucleotide therapies into the large population diseases, the challenge of supplying the required quantities of drug substance is now significant. Therapeutic oligonucleotides are generally manufactured for clinical and commercial applications using phosphoramidite chemistry on a solid support. This solid-phase chemistry is well understood and has been used for decades. It can deliver high-quality oligonucleotide drug substances, but the solid-phase process is neither readily scalable nor environmentally friendly. In 2016, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable identified the development of a greener process for oligonucleotides APIs as a critical unmet need. Many groups, including CatSci, are researching novel alternatives to solid-phase synthesis that can deliver an improved process with reduced waste, lower demand for acetonitrile, and improved atom efficiency.

You're clearly excited about oligonucleotides, but do any other innovative areas spark your interest?

I am excited about CRISPR, which has been used to knock out harmful mutant genes and to fix errors in coding sequences. In November 2021, the first base-editing therapy moved towards the clinic when Beam Therapeutics received FDA approval for an Investigational New Drug application to treat sickle cell disease (SCD). The BEAM-101 therapy uses base editing to reactivate the expression of fetal hemoglobin in autologous hematopoietic stem cells and is envisioned as a one-time treatment for SCD.

Other companies are developing CRISPR technology for cardiovascular diseases, transthyretin (ATTR) amyloidosis, leber congenital amaurosis 10, SCD, Beta-thalassemia, cancer, and diabetes. I await all future developments with great anticipation!

Best Practice

Technology
Quality
Compliance

A Roadmap to Greener Pharma Logistics

Pharmaceutical logistics by its nature creates sustainability challenges. There are opportunities for improvement, however, across warehousing, transportation, and packaging activities.

By Julius Graf von Pfeil, Head of Supply Chain and Finance, and Kees Schmidt, Head of Operations and Customer Service, both at Logistics4Pharma

Pharmaceutical research and development, manufacturing, storage, and distribution impact the environment in numerous ways from water and energy consumption to carbon dioxide generation. As the consequences of climate change become increasingly evident, industries worldwide are examining their environmental performance, with many global corporations establishing sustainability goals and implementing sustainability strategies. The pharmaceutical industry and members of the pharmaceutical supply chain are no exception; given that the sector produces more greenhouse gases than the automotive industry (1), the need to reduce environmental impact is crystal clear.

Most major pharmaceutical companies have nominated 2030 as their target for achieving carbon neutrality (2). In addition to reducing CO2 emissions, many have also established goals for lowering their generation of waste and consumption of water and energy. Some solutions being employed include recycling, greater use of electric vehicles and renewable energy sources, reduced use of plastic, and the modernization of facilities, using state-of-the art equipment and technologies.

As a first step towards achieving these goals, many companies are conducting environmental sustainability assessments that evaluate existing practices in comparison to the guidelines outlined in ISO 14001, an international set of standards for designing and implementing effective environmental management systems (3). Some companies are also using ReCiPe 2016 – a method built on a set of mathematical models that use inventory data to perform environmental life-cycle impact assessments (4).

Such assessments can be applied to every aspect of the pharmaceutical supply chain, including logistics activities (including low-temperature storage, packaging, and shipment by land, air, and sea). The assessments often focus on carbon footprint, but some also account for other important factors, such as damage to human health and ecosystems, as well as levels of resource consumption (5). Regardless of the method, these assessments highlight the environmental impact of pharmaceutical logistics activities, which helps identify realistic next steps – however incremental – that improve the environmental sustainability of the pharmaceutical supply chain.

What you can do

The rapidly expanding cold-chain logistics market is a key driver in the need for a greener pharma industry. Many current drugs and vaccines on the market – and an even greater portion of those in the pharmaceutical pipeline – require temperature-sensitive materials that must be handled, stored,

"One oft-overlooked mechanism for reducing the environmental impact of pharmaceutical logistics is to minimize the size of packaging systems."

and shipped at low temperatures (typically 2–8 °C, but sometimes as low as -80 °C). As a result, experts have estimated that the global pharmaceutical cold chain logistics market will expand at a compound annual growth rate of 9–15 percent for the next 5–10 years (6, 7).

By 2018, there were already four million refrigerated vans, trucks, semi-trailers, and trailers in use worldwide – as well as approximately 1.2 million refrigerated containers for reefer ships (8).

Despite the growth of cold-chain needs, there are many areas across the pharmaceutical supply chain where actions can be taken to reduce the environmental impacts. Temperature-controlled warehouses consume significant energy; however, state-of-the-art cooling systems and ventilation solutions can ensure optimal operation and minimize energy consumption. Though these approaches can require high financial investments that offer no immediate returns, they do provide measurable long-term benefits. Other smaller steps can also help reduce the carbon footprint of warehouse operations; for example, automated lighting systems and the use of renewable energy sources, such as wind and solar power.

One oft-overlooked mechanism for reducing the environmental impact of pharmaceutical logistics is to minimize the size of packaging systems. Space-efficient packaging solutions are often more economical, lighter, and allow the storage and shipment of more drug products in less space, thus reducing both costs and energy consumption. In cases where a proper return loop can be established, multi-use packaging has been used for products that require strict temperature-controlled conditions, increasing the sustainability of pharmaceutical logistics.

There is also room for improvement in terms of transport solutions. Low-carbon-footprint fuels can be used for the transport and distribution of pharmaceutical products. Experts have estimated that the use of biobased fuels can reduce greenhouse gas emissions by up to 90 percent compared with regular diesel (9). Compressed natural gas, liquefied natural gas, liquefied petroleum gas, biomethane, and bio-LPG are other alternatives.

Another more sustainable transport option involves the grouping of transport, when doing so does not impact quality or regulatory concerns. Applying algorithms that identify optimum routes with minimal carbon footprints is another. Technological advances in the design of transport refrigeration units will also have a positive impact.

In general, reusable containers can

Julius Graf von Pfeil

Kees Schmidt

be deployed more than 50 times. Upon combining this capability with efficient return logistics solutions, it is possible to support nearly 25,000 pack-outs, providers, and ultimately patients with just 500 packaging solutions (2). It should be emphasized that to be truly reusable, the system for returning the packaging must not place any measurable burden on the recipients of these packages. Return logistics solutions must also be cost- and energy-efficient.

Many of the most advanced passive cooling packaging solutions are constructed with state-of-the-art lightweight insulation materials. These solutions have demonstrated an energy demand as much as 50 percent lower than single-use solutions, as well as the potential for significantly reduced water depletion and waste generation (2). Furthermore, active reusable packaging systems (shippers with embedded sensors for digital tracking) not only provide real-time data on the condition and location of pharmaceutical shipments, but also achieve greenhouse gas emissions as much as 90 percent lower than passive shippers (9).

"Going forward, new technology could also help provide further gains in sustainability."

Going forward, new technology could also help provide further gains in sustainability. For example, with new automated loading software, the space in trucks and containers can be pre-organized with regard to storage conditions to reach the optimal capacity. The picking management in warehouses can also be made more efficient with the usage of augmented reality glasses that show the shortest route for the picker. Similarly, the introduction of innovative packaging materials and shipping container designs has the potential to reduce the environmental impacts associated with the storage and shipment of life-changing and life-saving medicines. Some examples include thermal covers designed to reflect sunlight, isolate the goods, and prevent air exchange.

Change starts in-house

Given the regulatory challenges and high investment costs associated with many activities that can boost environmental performance, it is often best for companies with restrictions in their financial and human resources to begin their sustainability efforts with a focus on internal activities.

Key examples include the recycling

Competing Obligations

Implementing new technologies and solutions designed to improve the sustainability of pharmaceutical logistics practices must not impact drug product quality or in any way conflict with GDP guidance and the numerous regulatory requirements that govern the handling, warehousing, and transportation of pharmaceutical products.

The greatest limitations concern packaging. Some pharmaceutical raw materials and drug products are highly potent and/or classified as dangerous goods. Typically, packaging that is close to drug products must be of food grade, resistive to damages and is often not available in recyclable forms.

Logistics service providers must also contend with the demands and expectations of their customers. Although many pharmaceutical companies are actively seeking ways to reduce their environmental impact, there are some cases where they insist on the use of a certain type of packaging because that format was employed in the stability or transportation studies conducted to support regulatory approval. Some customers might also be able to accept a certain product in a special packaging and not in any other.

There is, therefore, a constant struggle between the desire to reduce carbon emissions and resource consumption, and the need to maintain strict quality and safety standards.

Real-life action

At our company, Logistics4Pharma, we have drafted a five-year plan for achieving a set of specific sustainability goals that will benefit the environment, customers, and the company. In addition to increasing recycling and reducing waste generation, the company has also committed to implementing more advanced technologies and automation across its activities.

In 2022, we invested in the installation of a top-of-the-line compressor and cooling system for our temperature-controlled warehouse. The new system is designed to function with an advanced, biodegradable coolant, making it more ecologically favorable.

We also modified our warehouse lighting strategy to maximize the use of daylight and only use electrical lighting when necessary. Similarly, we installed more effective thermostats for regulating non-cooled areas of the warehouse, with automated controls programmed for maximum efficiency installed wherever possible.

To be effective with our energy usage, sensor technologies were deployed in all areas of our temperature-controlled warehouse. By mapping the temperatures in the warehouse during different seasons we are able to identify the areas that experience the greatest extremes in temperature during changing weather. Analyzing data from the sensors on a weekly basis enables us to track changes in temperature as they occur. This approach not only helps prevent temperature excursions – it also reduces high energy peaks. This is achieved by proactively adjusting temperature set points to warehouse specific values that ensure energy efficient operation of cooling equipment.

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of paper, cardboard, plastic, and other materials to reduce waste. Use of recycled materials, wherever possible, is also preferable, but even when that is not possible, waste can be recycled, reused or routed for use in other industries.

The next level of commitment to sustainability involves financial investment in new technologies to reduce resource consumption, waste generation, and carbon dioxide emissions; for example, replacement of outdated and inefficient cooling systems for warehouses, automated lighting solutions in various facilities, more advanced transport refrigeration units and refrigerated vehicles, and the latest cold-chain packaging solutions.

Though implementing sustainability strategies in the transport and packaging of API and finished drug products can prove challenging, there are still benefits to be gained by investing time and effort into developing optimum solutions.

The overall goal of pharma logistics must remain as "the efficient and on-time delivery of customer materials in accordance with all pharmaceutical and transport regulations to maintain quality and safety" – but this can and should be done while reducing your company's carbon footprint, resource and energy consumption, and waste generation.

Know thyself

It is essential to understand each shipment's needs, limitations, and associated risks before proposing options that will address those needs, overcome obstacles, minimize risks, and maximize sustainability. Good logistics service providers should be clear about where their strengths lie, and willing to speak up when they think customers are taking the wrong approach.

The provider should be clear on the options for consideration – whether for quality and safety, cost, or environmental reasons. It is also important to know where each provider's strengths lie. For instance, we are conscious of the fact that our own company is a smaller firm focused on supporting specialty logistics solutions, and therefore our own particular goal is not to be highly scalable but to take on project shipments that are tricky or require detailed attention. Having a clear understanding of where each provider excels will help you to simplify the process, and solve logistics problems as sustainably as possible.

References can be found in the online version of this article available at: tmm.txp.to/greener-pharma

Afraid of Banality, Driven by Beauty

Sitting Down With…
Tirtha Chakraborty,
Chief Scientific Officer
at Vor Bio

Did you always want to be a scientist?
I was born and brought up in India and most of my early science lessons came from my father – a veterinarian turned scientist. He introduced me to a laboratory where he performed cell culture for vaccine research. It became as much a part of my upbringing as dinner table conversations. Personally, I am terrified of banality – day-to-day repetition. I like change and, for me, science and the arts are two extremely dynamic areas that naturally complement each other.

How do you combine art and science?
Art was also a very big part of my upbringing. Art and science are, for me, the two most beautiful things – although I will include sports as a close third! There is a pattern – you need to recognize the beauty in the pattern and strive for perfection. A "good enough" mentality is not going to solve the big problems. I'm fortunate to have extraordinary team members who subscribe to the same philosophy of seeing beauty in science. Science is an art in its own sense.

How does the artist in you manifest today?
I painted for many years when growing up, but now photography is my primary inspiration. I think photography is a powerful combination of both science and art; you need to understand the science of light, as well as the mechanics of your equipment. For me, science is the same as photography – visual intonations influence the way I do science. I don't like ugly science. There's a lot of it – and some of it even works – but I'm not going to work in an environment where that becomes the norm.

What big scientific moments have excited you recently?
At the risk of sounding a little obvious, the CAR T field is a great success story, but I also think its early success is a bit of an issue for cell and gene therapy because it has reached the point of "good enough." It sometimes feels like people don't want to change a lot in that field now, and there is a reluctance to understand the fundamentals of what drives both safety and efficacy for these living drugs. This highlights one of the internal struggles in a profession where we encourage the industry to try and push the boundaries.

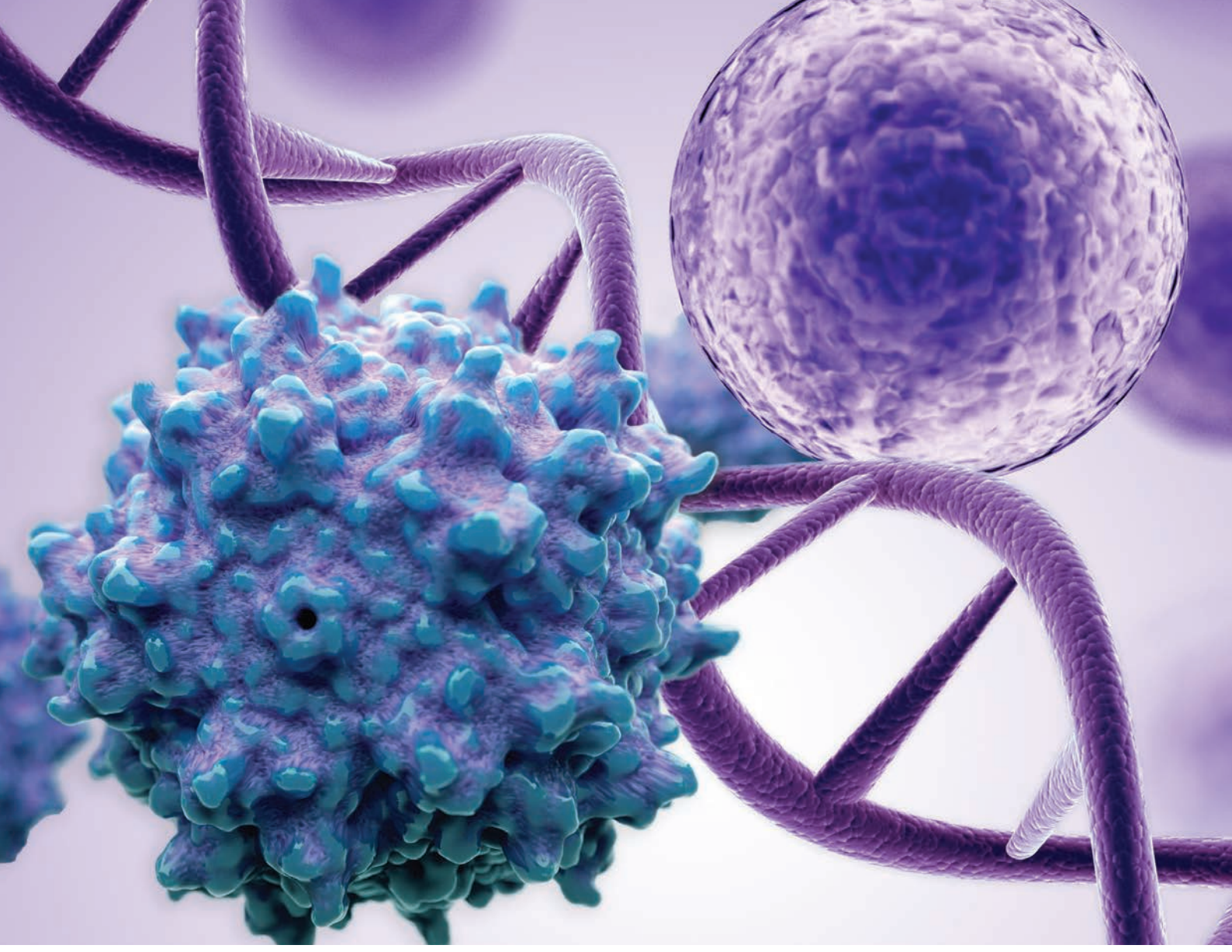
An area I'm excited about is gene engineering. I was very fortunate to be part of the team that led hematopoietic stem cell transplants based on gene engineering all the way from discovery to the clinic. Hematopoietic stem cell engineering is one of the most difficult things in science. To genome engineer cells and cure sickle cell or beta thalassemia patients – which has been done at a previous company I worked for, CRISPR Therapeutics – is science fiction that became science fact.

In what areas could we see breakthroughs in the future?
Whenever we talk about cell and gene therapy, the three most important things are delivery, delivery, and delivery. Ex vivo gene therapy is getting pretty crowded – again thanks to everyone rushing to make another CAR T product. Intellia had an extraordinary breakthrough in liver-directed gene editing, but the delivery problems of being able to use it exactly where it is needed in vivo are not yet solved. The whole CRISPR field exploded because of the excitement around precision genome engineering. If the potential in this area can be realized, it will be a game changer, but I think the key is devising the right delivery technology for each application.

Most of our cells in the body never divide. Because of that, the genome repairing mechanism allows for only imprecise genetic changes. That is what first-generation genome editing technology focused on. Technologically and scientifically speaking, the biggest frontier we need to tackle is where we can make precise genomic changes in non-dividing cells of the body. That will open an entire new universe of therapeutics. With base and prime editing, I think we can get there, but it is not going to be easy. Alternatively, if we want to make precise genetic changes, we need cells that can divide to allow alternate repairing mechanisms to kick in.

What is Vor Bio's current area of focus?
We are focused on the treatment of hematopoietic diseases, starting with hematopoietic malignancies such as acute myeloid leukemia, and are making next-generation hematopoietic transplants that are shielded from targeted therapy. We hope these products could become the standard of care in the near future. For this application, we are genome engineering hematopoietic stem and progenitor cells. Creating a stem cell transplant that provides universal protection from targeted therapy may open all kinds of treatment opportunities, and radically change outcomes for patients.

What should be the priorities of the advanced medicine space?
Education across the board. Advanced medicines like cell and gene therapies are still in their infancy, and it is vital to appreciate how radically different these drugs and the requirements during drug development are in comparison to decades of the existing paradigm. Drug development in advanced medicines has no template. We are the ones creating the template. The quality of science and the quality of scientists who need to drive these priorities are very different now from what they were 20 years ago, so the industry needs to focus on hiring the best brains in the world rather than letting the best brains go into only academia!



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