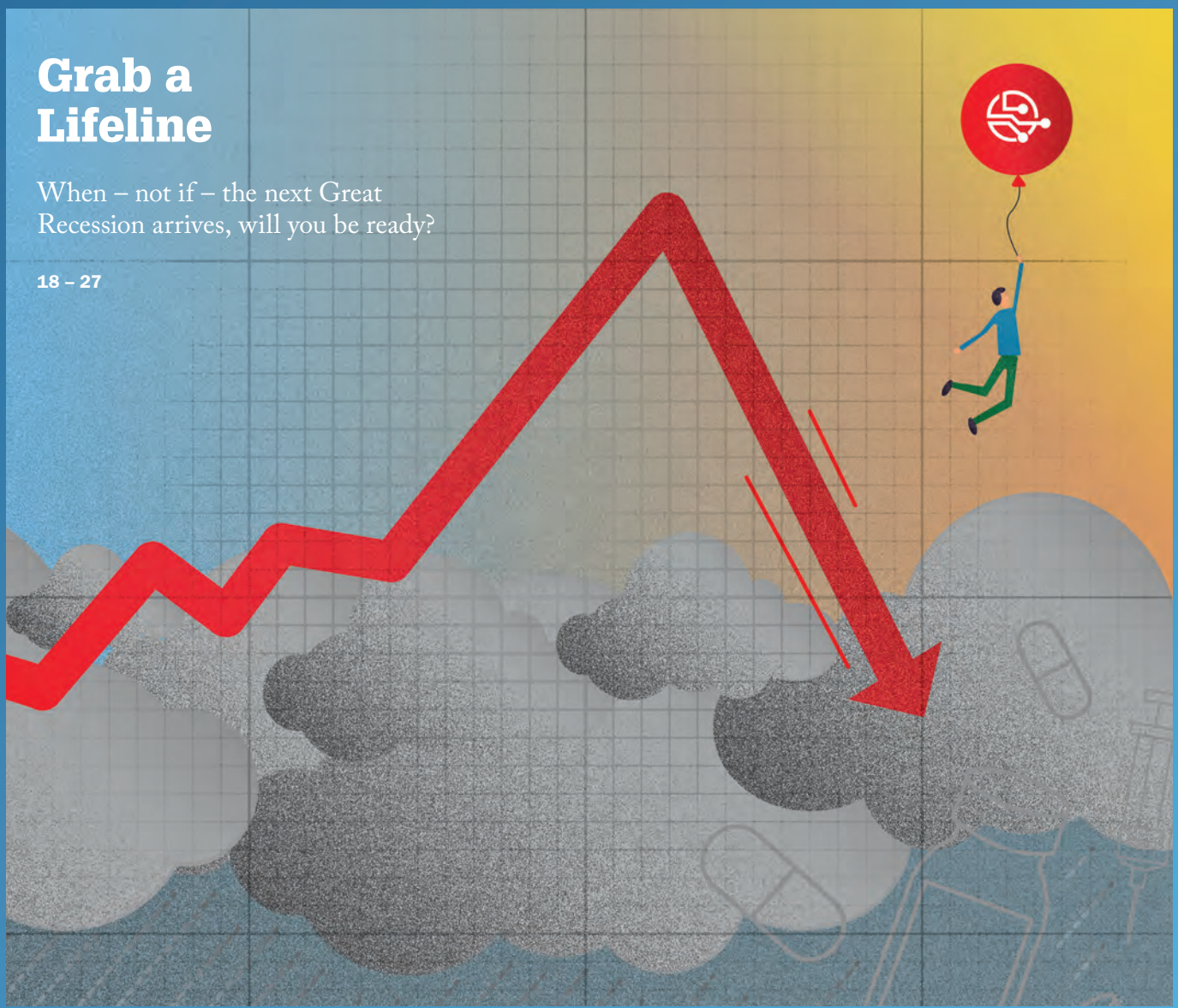
JANUARY 2020 # 61

the Medicine Maker™



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Online this Month

Vote Now for The Innovation Awards!

At the end of 2019 we celebrated The Medicine Maker 2019 Innovation Awards. From traditional small molecules to biotherapeutics to ingenious cell and gene therapies, there is a huge variety in the types of medicines that pharmaceutical companies can produce, with each requiring differences processes and equipment. The innovations highlighted in the Awards demonstrated vendors' dedication to cater to all areas of drug development with new solutions.

But which technology is truly the most innovative? Out of the 16 selected technologies selected for the Awards, we want you to vote for the one you believe is the most groundbreaking. Register your vote at http://tmm.txp.to/vote-innovation19.

Voting will close on March 11, 2020.

Top Innovations of 2019:

- ACGcaps H+
- Avionics
- BioContinuum Buffer Delivery Platform
- ChargePoint Multi-Site Solution
- Everic
- F10i
- HR Multi-Attribute Method for Biopharma Analysis
- HyPerforma DynaDrive
- InfinityLab LC/MSD iQ
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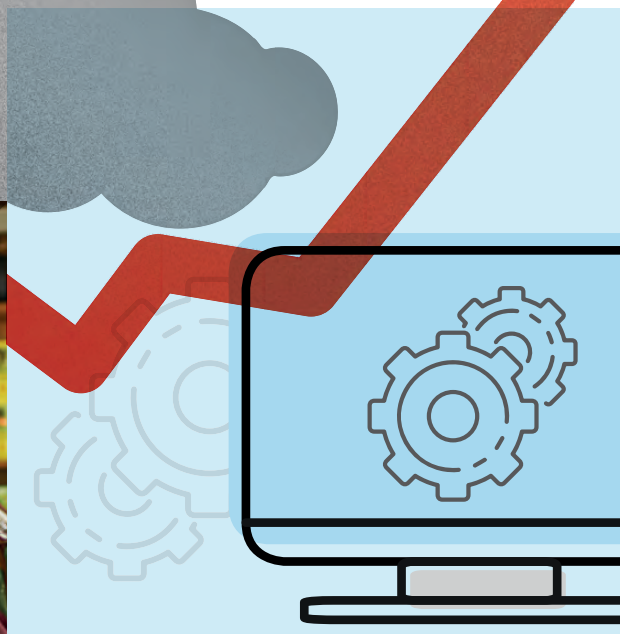

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On The Cover

Is pharma prepared for the next Great Recession?

NextGen

Profession

Sitting Down With

the Medicine Maker

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New Decade, New Hope

The "cures for all" concept presents a clear focus for the next decade – but companies must be rewarded for their work

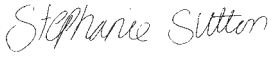
The last decade was pretty amazing for pharma, with cell therapies being the stand out stars of the show. The industry has proven that these groundbreaking treatments can be made and delivered to patients – opening the floodgates to research and development activity that will surely bear fruit in the next decade. Since 2010, other phenomenal treatments have also reached the market. Consider sofosbuvir – Gilead Sciences' cure for hepatitis C – as one example of a drug that has radically changed the lives of patients.

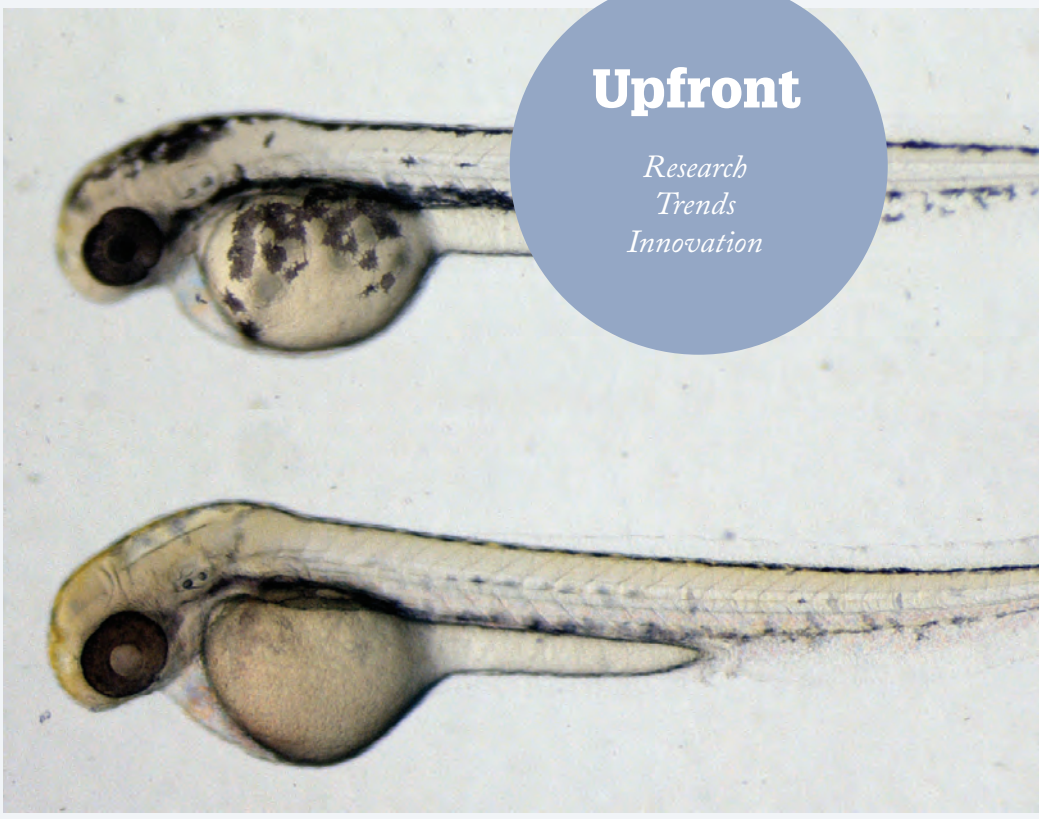
As debates around drug pricing continue, we must find new ways to reward and incentivize true innovation in pharma. When it was first approved, sofosbuvir ignited enormous controversy because of its huge price tag. Just three years after the launch of sofosbuvir, however, Gilead began to see significantly less profits within its hepatitis C revenues; sofosbuvir is so effective that there are simply less patients to treat, which is clearly a good thing. And so, we need to ensure that companies have good reason to develop disruptive therapies – even when doing so shrinks their own market. In short, there must be a clear business case for cures. When there isn't, it is damaging for the whole of society – consider the vaccine space, where low profits have led to a lack of new vaccines.

The industry will also need help to improve in other important areas. Take biosimilars, where progress appears to be painfully slow. The first biosimilar was approved in Europe by the EMA in 2006. Meanwhile, the FDA approved the US's first biosimilar in 2015. In mid-December last year, WHO prequalified its first biosimilar – trastuzumab, supplied by Samsung Bioepis NL BV (the Netherlands). The medicine is now eligible for procurement by United Nations agencies and national tenders, which will help to finally bring a biosimilar to the world's poorest people – 13 years after the first biosimilar was approved in Europe.

With that in mind, how long will the world's poorest be waiting for cell therapy treatments? Or will they never gain access? The onus should not be on the WHO alone to help make medicines more widely available; big pharma companies and governments need to work together to drive real innovation that pays.

Stephanie Sutton
Editor





Fungal (Library) Growth

Time to mine the biologically active compounds of fungi

Thousands of biologically active secondary metabolites derived from different types of fungi have been analyzed and assigned to a library in a joint effort between the Hubrecht Institute, the Westerdijk Fungal Biodiversity Institute and Utrecht University in the Netherlands.

"An aging global population and the growing issue of drug resistance means that we need better and newer drugs, but the number of chemically distinct compounds that are being used in prescription drugs is limited. In addition, the active compounds in these drugs are often chemically related, relying on similar mechanisms to function," explains research leader, Jeroen den Hertog from the Hubrecht Institute. "Fungi are known to produce pharmaceutically relevant compounds. And despite there being an estimated two million species of fungi, only a small fraction has been analyzed for their expression of biologically active compounds to date."

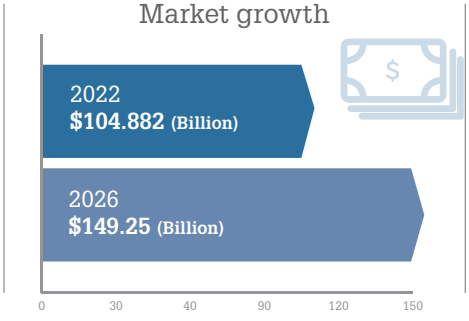
The fungal kingdom has remained relatively unexplored in part because access to pure and uncontaminated fungi is limited, making it difficult to assess their bioactive properties. And that's why Den Hertog and his team were given access to the Westerdijk Institute's collection of live fungi strains. Using the strains as a starting point, the team produced 1526 filtrates that had biological activity. Among the discoveries, the team found that Resinicium furfuraceum produced the cholesterol lowering drug lovastatin – the first time this fungus has been shown to produce the drug.

The team is also investigating fungi that induce developmental defects in zebrafish, as well as how fungi could help produce new antibiotics. "Using the library that we have generated, we can now screen for the biological activity of fungi using a variety of bioassays," Den Hertog says. "Further to our initial investigation, we have screened compounds for their antimicrobial activity and found hundreds of fungi that produce compounds that demonstrate antimicrobial activity against multiresistant, pathogenic strains of bacteria."

INFOGRAPHIC

The Pack of the Future

How can pharmaceutical packaging be adapted to meet patient and supply chain requirements?



PHARMA PACKAGING IN BRIEF

Acquisitions, market growth and global trends… We examine what's going on in pharmaceutical packaging

- Faller Packaging, a specialist in pharmaceutical packaging, has acquired the Hungarian manufacturer of pharmaceutical leaflets, Pharma Print Kft, in a bid to expand its production capabilities across Europe. Faller now has eight locations in its European network. "Our new location will give us additional expertise and capacity in the manufacture of leaflets, and it will help us to serve our customers with even greater speed, breadth of support and reliability," a spokesperson from Faller said.

- The recent growth in popularity of biologics and biosimilars has resulted in significant market growth for the pre-filled syringe space, with the sector expected to reach a projected value of $9.53 billion by 2026. The rise in the number of infections and injuries caused by needle sticks in hospitals has led to increased interest in pre-filled syringes as an alternative.

- West Pharmaceuticals and Schott have announced their intention to combine the SCHOTT iQ Platform with West's Ready Pack System. The partnership will allow the companies to provide customers "with high-quality glass containment options to complement the stoppers, seals and glass alternatives". The partners plan to use their collaborative platform to meet other customer requirements, including batch size management and containment systems for biologics.

Last Chance Nominations

The 2020 Power List: nominate the best and brightest that pharma has to offer before it's too late

The deadline for nominations for The Medicine Maker 2020 Power List is fast-approaching! This prestigious list will celebrate influential people who have contributed to the pharma industry's success and progress over the years in three categories:

- influencers in the small molecule drug industry
- influencers in biopharmaceuticals
- influencers in cell and gene therapy

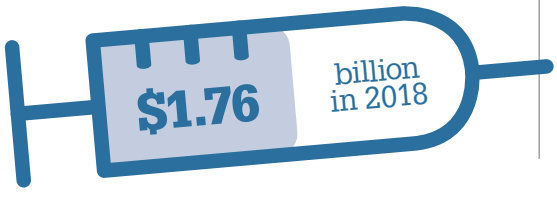
This year, only 60 of pharma's finest will make it into the final list, so start nominating those you feel are the most worthy. You can also nominate yourself if you wish.

Nominate at http://tmm.txp.to/pl2020-noms but be quick because nominations close on February 3 2020.

The final list will be published in April 2020.

Primary packaging

Europe is slated to dominate the prefilled syringes market share. Market size stood at



Temperature controlled packaging

Solutions were worth **$3.33 billion** in **2018** and projected to reach **$5.94 billion** by **2026**, growing at a CAGR of **7.49%** from **2019** to **2026**.

USA, Europe, Japan, China, India, South East Asia are leading market growth

The Industry Strikes Back

How digital technologies are helping to secure the pharmaceutical supply chain

Chinks in the pharmaceutical industry's armor have allowed fake and counterfeit drugs to become a significant problem. Here, we speak to Bright Simons, President at mPedigree, a non-profit organization that wants to build a new ecosystem to fight fake medicines, to find out how digital technologies combined with pharma packaging schemes are helping to address the problem.

mPedigree uses mobile and web technologies to help secure pharmaceuticals against counterfeiting and diversion. Manufacturers can upload pedigree information about their products onto a centralized registry that works as an RFID-enabled serialization platform, helping to facilitate communication between stakeholders in the supply chain.

What challenges does the supply chain face?

Gray marketing and a lack of specialized incoterms has resulted in confusion over laws and standards from country to country. At a regional level, such as in Africa and South Asia where mPedigree does most of its work, this has led to fragmented data management and surveillance initiatives, which can create opportunities for counterfeiting or product diversion.

A number of solutions and initiatives have been adopted to combat the counterfeit problem, but getting small and medium-scale enterprises – as well as the heavily under-resourced public agencies – across Africa and South Asia on board with supply chain initiatives requires the creation of "local bridges" to global standards.

How are digital technologies helping to fight fake medicines?

Simply put, they provide connectivity. Digital technologies offer us all the tools we need to facilitate real-world partnerships to solve the problem of fakes holistically by enabling connections among industry, retailers, wholesalers, consumers, regulators, independent institutional observers and regulators/law enforcement authorities.

How is mPedigree helping to address the problem?

We use a direct-to-consumer model, which allows patients and customers to:

- log medicines at the tail end of the distribution
- provide unit-level feedback
- provide their opinions on pharmacovigilance
- help curate market intelligence by labeling data points provided in-app
- close the track-and-trace chain by authenticating the serialization ID on the medicine pack

Beyond technology, we also work to design protocols and influence legal-regulatory mechanisms. Ultimately, our goal is to fight back against mainstream thinking by working with partners around the world to demonstrate the power of ecosystemic solutions.

Generation AI

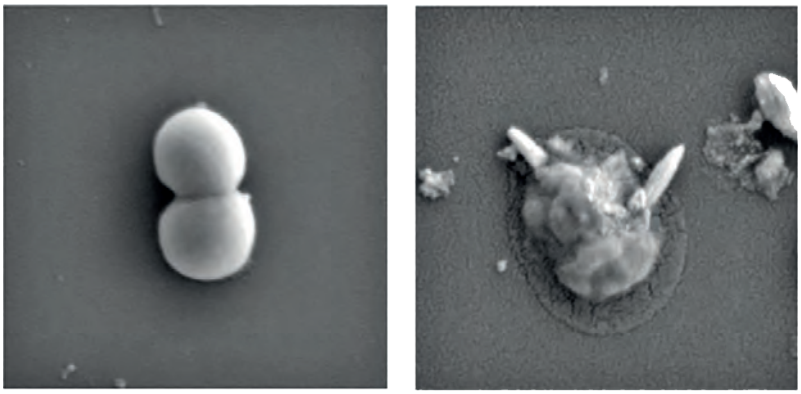
Is AI turning the tide for next-generation peptide therapeutics?

Pharma is (slowly) being redefined by artificial intelligence (AI) and machine learning platforms. From clinical trials to the manufacture of drugs, these technologies give the industry the opportunity to enhance its practices and remove the risk of human error. Mytide Therapeutics, a Boston-based biotech company, has recently been using AI for the development of peptide therapeutics.

"Peptides are the foundation for a variety of next-generation therapeutics, particularly within the immuno-oncology space. There are a number of companies that are having a great deal of success in bringing this type of therapeutic into clinical settings, but a major challenge in doing so is scale up. For each peptide-based vaccine, 20 to 30 peptides are required – and because these are often personalized medicines, manufacture is dependent on the tumor site within patients," explains Dale Thomas, cofounder of Mytide Therapeutics.

He believes that AI platforms can help cut the lead time of manufacturing processes from months to under a week. Other technologies, such as robotics to automate each step of the manufacturing process, could also help. Read more at www.themedicinemaker.com.

IMAGE OF THE MONTH



Gold Crush

Attempting to curb antibioitc resistance, researchers at RMIT Univeristy, Melbourne, Australia, have developed a technique using liquid metals to shred bacteria, preventing them from thriving without harming normal cells.

RMIT University

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Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"If we launched more medicines, we'd create a genuinely competitive environment, where success is driven by more than exclusivity – by innovation in commercial models and truly reflecting unmet need in choices of outcome measures and patient relevance."

Mike Rea, Power List 2019

Synthetic Silos

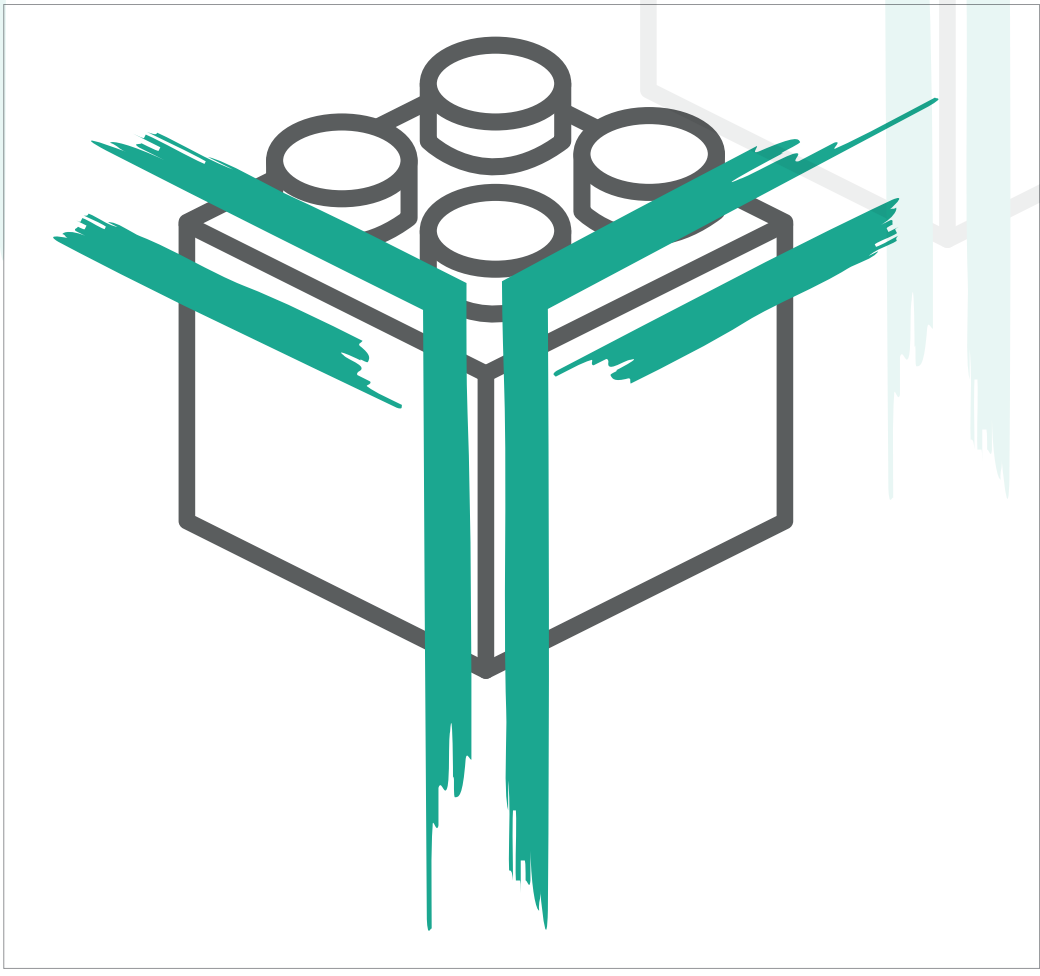
3D-printed water-in-water constructs mimic cell compartmentalization with potential in drug delivery

A project funded by the US Army Combat Capabilities Development Command (CCDC) has resulted in a material system that could be used to deliver medicine, treat wounds, and purify water for soldiers in the field. Developed at the University of Massachusetts Amherst, the eco-friendly, synthetic system mimics biological transport and compartmentalization in cells by creating a structured water-in-water environment using water soluble and oppositely-charged polyelectrolytes – with targeted drug delivery presented as one potential application.

By eliciting chemical gradients in the system, biologically relevant compounds can be transported through and/or directly released from the compartments. The researchers believe that this might make the system useful for keeping fragile therapeutic molecules sequestered and safe under storage conditions, and allow for the release of these molecules when needed.

LEGO Linkers for ADCs

How to design more stable and predictable antibody-drug conjugates



Antibody-drug conjugates (ADCs) couple the potency of a cytotoxic agent with the selectivity of an antibody. But despite early promise of the technology, only five ADCs have received market approval to date (we explored the potential of ADCs to move to the forefront of the targeted therapy space at tmm.txp.to/ten-adcs). In an effort to develop more stable and predictable ADCs, an investigational team based at the Brigham and Women's Hospital in Boston, US, has been using computational simulations to focus on improving a crucial element: the linker (1).

"Our goal is to engineer next-generation treatments for unmet medical needs from simple building blocks and strategies that facilitate rapid translation to the clinics. ADCs fall into this category as they leverage existing technologies," explains team leader Shiladitya Sengupta, Associate Bioengineer at Brigham and Women's Hospital and Associate Professor of Medicine at Harvard Medical School. "The challenge in bringing them to market lies in the linker technology used to create them." Classic linkers rely on covalent interactions, which can easily "fall apart" in circulation and limit the choice of payload; the researcher's paper, published in Nature Biomedical Engineering, notes that Mylotarg, an FDA-approved ADC, loses 50 percent of its toxic payload within two days because of the older generation linker technologies used to hold it together.

Using molecular docking and molecular dynamics simulations, the team designed a LEGO-like linker that allowed drug payloads and antibodies to self assemble into ADCs. "The self-assembly we observed inspired us to name our approach MAGNET ADCs," said Sengupta, noting the origin of the acronym: "multivalent and affinity-guided antibody empowerment technology." Even though MAGNET ADCs are held together by weaker, non-covalent bonds, the high specificity results in increased stability. To prove the point, the Boston-based team put their MAGNET ADCs to the test in a model for human lung cancer, showing that they could maintain stability for up to 14 days and with low levels of toxicity in vitro.

"Though we tested our technology in a model for lung cancer, the therapeutic and diagnostic applications of MAGNET ADCs are varied. Our MAGNET-linkers target conserved sequences in the antibodies and, therefore, any antibody can be used to build an ADC. The possibility of targeting diseases beyond cancer is real," says Sengupta.

The team has now turned their focus to engineering drugs that activate B cells in cancer.

Reference

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In My View

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

Food for Thought

If we learn more about drug–nutrient interactions, we may be on the path towards better medicines

By Araksya Topchyan, Global Marketing Manager Pharma at DSM

Vitamins are considered safe until proven unsafe; whereas pharmaceuticals are considered unsafe until proven safe. The two follow very different development pathways and are subject to different guidelines and regulations, but both are produced with the aim of improving health. The benefits of pharmaceuticals must be proven for them to reach the market, but for vitamins and lipids, there are still some debates about their role beyond nutrition. We do know, for instance, that vitamins and minerals are essential for health, as deficiencies can lead to disease (consider scurvy or rickets). But is there also a link between vitamins and their interactions with pharmaceuticals? When considering adverse drug interactions, drug-drug interactions typically come to mind, but interactions between drugs and nutrients also exist – and they can be both positive and negative.

Drug-nutrient reactions (DNIs) are defined as alterations in the pharmacokinetics or pharmacodynamics of a drug or nutritional element, or a compromise in the nutritional status of an individual as a result of drug intake. To determine the impact of drugs on patient health, DNIs can be loosely classified into the following categories:

- Class 1: effect of obesity and malnutrition on drug action
- Class 2: effect of nutrition on drug action
- Class 3: effect of specific nutrients or dietary supplements on drug action
- Class 4: effect of drugs on nutrition status
- Class 5: effect of drugs on nutrient status

Understanding and addressing DNIs is particularly relevant as the population ages. With more individuals experiencing multimorbidity, polypharmacy is becoming more prevalent. Currently, the populations most at risk of DNIs include elderly people, patients with chronic conditions, individuals who are malnourished, pregnant women, and infants.

Importantly though, new research also suggests emerging therapeutic benefits for vitamins and lipids in selected individuals and population groups (1), which may mean that DNIs could have positive effects and benefit patient health in some cases.

Vitamins and lipids are molecules that humans receive primarily through food intake. Their role, by nature, is to maintain important processes in our bodies, as well as support overall health and wellbeing. Increasingly, questions are being asked about how vitamins and other nutrients are linked with disease. More research is evidently required, but from our cooperation with clinical researchers around the world, we know that vitamins and lipids can possess therapeutic effects in disease conditions.

Several associations have already been made between certain drugs and nutrients, which continue to shape future research in the field; for instance, interactions have been observed between statins and EPA and DHA fatty acids – here, statins may alter the balance of omega-3 and omega-6

"We need to generate more evidence about the role that vitamins and lipids play in disease management."

fatty acids in the body (2). Examples of where other common DNIs occur include contraceptives and folate, proton pump inhibitors and vitamins C and B12 and metformin – for type 2 diabetes – and vitamin B12.

As a more detailed example, lower back pain is one of the world's most common ailments and the second most frequent symptom-related reason for outpatient visits after the common cold. To treat lower back pain, non-steroidal anti-inflammatory drugs (NSAIDS) are typically prescribed to patients. Although NSAIDS have a well-established efficacy and safety profile, recent research highlights the potential role of vitamin B complex (i.e., vitamin B12, vitamin B1 and vitamin B6) as an adjunct to NSAID therapy (3). Though the exact mechanisms for vitamin B complex efficacy in the treatment of lower back pain are still largely unknown, the prevailing hypothesis involves increasing afferent inhibitory control of nociceptive neurons at the spinal cord, improving sensory nerve conduction velocity, and reducing neuronal hyperexcitability by altering sodium currents in injured dorsal root ganglia. In combination with NSAID therapy, vitamin B complex has the potential to produce synergistic effects.

Other interactions that could prove beneficial to patients include the addition of EPA and DHA in conjunction with conventional cytotoxin therapies for cancer; results have shown a two-fold increase in therapy response rate and clinical benefit when compared to patients undergoing the same treatment without supplementation (4).

In my view, pharmaceutical and healthcare communities need to be more aware of the potential relevance of DNIs. To avoid putting patients at risk, drug developers should take more responsibility by including drug–nutrient evaluations as part of the drug development process or communicating new information about DNIs to healthcare professionals, so that they can give the best medical advice to patients.

"The importance of improving our understanding becomes evident when you consider the benefits of minimizing harmful DNIs, or promotion of beneficial interactions."

In addition to this, we need to generate more evidence about the role that vitamins and lipids play in disease management – and this may open up new opportunities for drug developers to innovate and bring new therapeutic applications to the market. Vitamins and lipids are already proven and safe molecules with new science continuously supporting their evolving benefits in patient care and health. Understanding and leveraging the potential role of vitamin APIs and lipids as intermediates therefore offers an avenue for fast, safe and cost-effective innovation.

The importance of improving our understanding becomes evident when you consider the benefits of minimizing harmful DNIs, or promotion of beneficial interactions:

- Medications achieve their intended effects
- Improved compliance to medication
- No need for additional medications or higher dosage
- Reduce adverse side effects and disease complications
- Manage co-morbidities in chronic patients
- Reduce the burden and costs on the healthcare system.

Chronic patients are most exposed to DNIs and, with the aging population, we know that the number of individuals who will experience chronic illness will increase. Therapeutic areas, such as diabetes, cardiovascular disease, inflammatory bowel disease and pain, are where we think collaborations with partners in the pharmaceutical industry will be most beneficial. In these areas, we hope that by transferring our knowledge of DNIs onto drug developers, we will inspire effective patient solutions.

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For the Many

The pharmaceutical industry must be encouraged to look beyond patients in advanced economies to all patients who could benefit from innovative medicines, no matter where they live

By Charles Gore, Executive Director of the Medicines Patent Pool

Trying to fathom the frustration felt by a mother who is unable to afford her child's life-saving drugs is difficult in the extreme. But during my time with the World Hepatitis Alliance (before I joined the Medicines Patent Pool), I was faced with just that situation. I met a mother who had sold everything she owned to help purchase medicines for her son, but she still had a long way to go to give her child the drugs he so desperately needed.

And it's far from an isolated case. Over 2 billion people worldwide don't have sufficient access to essential medicines and health products. Those of us who have been involved in patient advocacy anywhere will not be unfamiliar with the feelings of frustration and failure in not being able to help such patients in meaningful ways. So how do we move forward?

In the early days of public health organizations like the Medicines Patent Pool (MPP), the focus was solely on facilitating access to drugs to treat specific conditions like HIV in developing countries. Though this was a critical initiative that has resulted in millions of people getting access to medicines they need, it failed to recognize that patients (including some of those same people on HIV treatment) were still waiting for many other essential medicines to become affordable.

I strongly believe that no new drug should be launched without a plan that outlines how patients everywhere stand to benefit. Traditionally, the pharmaceutical industry has developed drug launch plans for the countries where they stand to make the most profits. And then, at a later date, they may expand those plans to include countries in the developing world. This can leave people in the developing world feeling as though they are merely an afterthought.

Fortunately, global public health is becoming an area of increasing attention, and the resulting debates and discussions are helping to structure a roadmap for improved medical access. The World Health Organization has contributed to identifying those medicines (as well as diagnostics) that are deemed essential to meet the priority healthcare needs of populations. And tools like the Access to Medicines Index are becoming increasingly important for the pharmaceutical industry; they help identify best practices and highlight those companies taking positive action. Such tools also have the added incentive of improving the perception of an industry that has been plagued by bad press for decades. According to the Access to Medicines Index rankings, GlaxoSmithKline, Norvartis and Johnson & Johnson are proving to be frontrunners in issues associated with R&D and pricing – helping to set a precedent for the rest of the industry. Novartis, for example, has said that it will not launch any new drug products without an access program – a bold and welcome move that should help people in the developing world feel that they are no less important than those in high-income countries.

Despite the positive steps forward, the need for multiple sources that are capable of producing high-quality drug products for patients in low- and middle-income countries is still very much apparent; in this regard, creating more competition from generics can help. And so, at the MPP, we partner with patent holders for public health driven licenses that enable the sublicensing of drugs to companies who can focus on the sale of generic drugs at more accessible prices in developing countries.

Today, more now than ever before, companies are showing their willingness to engage with us. But there are still many who lag behind – in some cases, worried that public health licensing could come at the expense of their growth. This certainly need not be the case. The objective of organizations like MPP is to help companies reach as many people as possible with their innovative

"I strongly believe that no new drug should be launched without a plan that outlines how patients everywhere stand to benefit."

medicines in a way that is win-win. In fact, there is a good business case for our model and as more companies sit down with us to have in-depth discussions, they are coming to understand what public health licensing can do for them as well as for patients.

Access is part of the zeitgeist – because universal health coverage will be unattainable for many countries without it. We want the opportunity to help companies engage in thinking about access in the broadest sense. Our model is far from the only one and we have no interest in promoting it where it wouldn't work. For certain products it will work beautifully – as it has in HIV and hepatitis C – but for others it may not. What is important, however, is that companies should be aware of the full range of access options available to them so they can make the best choices that will maximize access to those who need it.

The Excipient of the Future

Advances in manufacturing aren't enough to overcome the challenge of poorly soluble APIs – we must also embrace novel approaches to excipients

By Dieter Lubda, Director of R&D Operations, Merck KGaA, Darmstadt, Germany

Oral administration remains the most convenient form of delivery for patients and healthcare providers, but the poor solubility and bioavailability of newer APIs have become major roadblocks for pharmaceutical development. It has been reported that up to 80 percent of new chemical entities under development today have poor solubility, resulting in limited oral bioavailability. Consequently, technologies that help companies overcome the inherent low solubility of many newly developed APIs have never been more important.

Although there are a number of approaches to improving solubility, bioavailability and dissolution rates, formulation technologies have, for the most part, remained unchanged for decades. The use of drug carriers (e.g., mesoporous silica), spray drying and hot-melt extrusion (HME), as well as improved production methods such as continuous manufacturing, can all have an impact, while personalized medicine, 3D printing, and amorphous solid dispersion look set to be the disruptive technologies of the future. However, new manufacturing techniques are not enough in isolation – we also need innovative formulations. A good example is mesoporous silica formulations, which have been shown to be excellent carriers for poorly water-soluble drugs. Though the concept was first introduced in the early 1970s by pharmacists Donald Monkhouse and John Lach, the technology and its applications are still relatively new to the pharma industry. I believe this is exactly the type of formulation innovation we as an industry need to embrace.

Right now, there is a huge demand for greater flexibility and efficiency. Continuous manufacturing is one solution, but one of the key drawbacks is the need for a relatively high amount of API in early development and increased sensitivity to changing API properties during the pharmaceutical development process, whereby changes in physical particle attributes may result in difficult and unreliable process development.

One potential way to overcome this issue could be realized through a more intelligent approach to excipient design. The use of API-loaded mesoporous silica instead of the pure API results in homogenized particle properties throughout the pharmaceutical development cycle. Ultimately, the API loaded onto the mesoporous silica will retain the same particle properties at all stages in process development. This allows robust continuous processes to be developed early on in the project, minimizing API requirements. This is just one example of how incorporating smart excipient strategies can lead to more efficient drug development.

"New manufacturing techniques are not enough in isolation – we also need innovative formulations."

The pharmaceutical industry is in urgent need of faster, more efficient and flexible solutions to produce oral medications. Instead, taking a holistic view when it comes to pharmaceutical advances will be the key to the industry's next and greatest successes. By combining advances in discovery, formulation, and manufacturing to produce the best and most robust products, true progress in drug development can be made.

THE NEXT GREAT RECESSION

THE USA WILL HAVE ANOTHER RECESSION – AS CERTAIN AS NIGHT FOLLOWS DAY – BUT HOW BAD WILL IT BE? AND IS THE PHARMACEUTICAL INDUSTRY PREPARED?

By George Chressanthis

"There will always be a business cycle, and white-collar workers will get hit in the next recession like they always do in recessions."

Robert Reich, American economist, Secretary of Labor 1993–1997

"The global financial crisis – missed by most analysts – shows that most forecasters are poor at pricing in economic/financial risks, let alone geopolitical ones."

Nouriel Roubini, American economist

The Great Recession, lasting from December 2007 through June 2009 in the US, led to a global recession in 2009, adversely affecting global pharma and healthcare markets (1, 2, 3, 4, 5, 6, 7). In the US, in particular, the Great Recession had a transformative effect on pharma – shaking the very structure of the industry. It is now considered more recession-sensitive than ever before, with cost-shifting from payers to the patient and the growth of expensive personalized medicines, often involving orphan drugs to treat rare diseases, adding greater recession sensitivity to drug demand (8, 9, 10, 11).

There are multiple signs that, despite 2018 ending on some good macroeconomic news, structural problems persist (12). Fears about the next recession in the US – which would have a knock-on effect in global markets – started in the summer of 2018 and really began to manifest in significant stock market volatility in December 2018, with continued risks being called out to this current day (13, 14, 15). In the US, the Federal Reserve ("the Fed") reduced the federal funds rate, a benchmark used for rates on credit cards and mortgages, by a quarter point at the end of July 2019 – seen by economists and market analysts as an expansionary move – in response to a growing fear about domestic and global economic and geopolitical conditions (16, 17). This action mirrors sentiments recently expressed by the Federal Reserve Federal Open Market Committee (FOMC) meeting in June 2019, which noted that risks to the future economic outlook were balanced, meaning there are both positive and negative signs in continued economic growth (18). Participants also expressed gloom about the global economic future at the annual Federal Reserve Economic Policy Symposium in August 2019 (19).

Economists surveyed earlier this year by The Wall Street Journal (WSJ) assessed a 25 percent and 57 percent chance for a recession in 2019 and 2020, respectively (20). Markets nervously reacted to the August 2019 US jobs report, noting that the numbers reflected a global slowdown occurring outside the US, stunting growth – likely caused by trade uncertainty created by the Trump administration (21, 22). The Federal Reserve finally announced a small quarter-point reduction in the discount rate to just above 2.0 percent on September 18, 2019, reflecting slowing economic growth in Europe and China, and the effects of global trade uncertainties that add to a drag on future growth prospects (23).

So, while the prospects of when a recession will start are uncertain, two key questions to ask are:

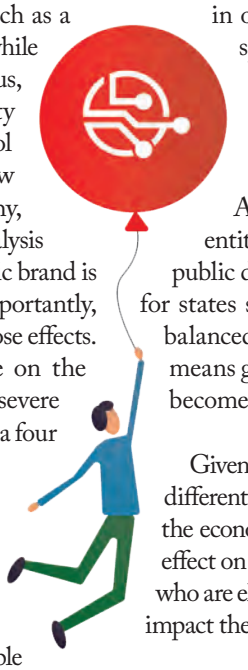
i. "How does a recession affect pharmaceutical drug demand?"
ii. "Are pharma companies prepared for this event?"

Or, put another way: have any lessons from the Great Recession experience been incorporated into future pharma business planning when the next recession occurs?

Shifting drug demands

There is an overall dearth of empirical evidence connecting the sensitivity of biopharma industry demand for specific drugs to a recession. Publicly available research literature tends to look at the effects of a recession on drug spending in the aggregate, which masks the different types of recessionary effects on drug demand relative to factors that can be affected by company actions, such as sales, marketing, payer contracting, and pricing. This comparison of effects is important since macroeconomic trends, such as a recession, are taken as a given to an individual company, while sales and marketing are under management control. Thus, building models that measure how the advent and severity of a recession can be mitigated by management control variables is important insight for executives. We know the Great Recession had different effects by geography, especially by specific region or metropolitan area. An analysis at a highly disaggregated geographic level and by specific brand is needed to understand true recession effects – and, importantly, how mechanisms available to executives can dampen those effects.

Using economic theory and practical experience on the determinants of pharmaceutical demand functions, a severe recession would have effects on specific drug demand via four empirically measurable mechanisms.



1) The disposable income effect

A reduction in real (inflation-adjusted) disposable income caused by falling or stagnant wages reduces affordability of (and access to) drugs. A decrease in disposable income relative to any out-of-pocket cost to access drugs will decrease drug demand. One should also see substitution effects in the proportion of biologics and branded drug demand relative to biosimilars and generics demand due to disposable income effects.

2) The unemployment/labor force participation/loss of insurance effect

Unemployment often results in a loss of patient health insurance. Since the Great Recession, the labor force participation rate (the number of people who are employed and unemployed but actively looking for a job divided by the total number of eligible workers between the ages of 16–64) in the US has stabilized at around 63 percent, a number not seen since the mid-late 1970s (24). The passing of the Patient Protection and Affordable Care Act (ACA) and the availability of health insurance through exchanges not connected to employment and subsidized premiums based on income may mitigate the effects from a poor labor market and declining access to employer-provided health insurance. The degree to which access to drug insurance through the ACA mitigates recessionary effects depends on the cost of premiums relative to people's limited income and the choice of plan.

3) The wealth effect

A severe recession may reduce the value of financial and physical assets; for example, changes in the value of equities and bonds versus changes in assets like the price of housing. People who are in or close to retirement may use these assets for future spending, thereby reducing drug affordability – similar in response to a disposable income effect.

4) The government effect

A recession depresses tax revenues, while increasing entitlement-program spending for the poor, which means public deficits will grow. In the US, this effect is more severe for states since governments at this level generally must run balanced budgets, causing pressures to reduce spending. This means government-provided health insurance programs may become more restrictive in their drug benefits.

Given that a severe recession produces varying consequences on different segments of the population based on their relationship to the economy (for example, a rising unemployment rate has little effect on drug demand for therapy classes dominated by patients who are elderly or retired individuals), the above four effects would impact the pharma industry in the following ways:

- Lower utilization of patented biologics and branded drugs, with greater sensitivity seen for more expensive specialty medicines (which should exhibit greater price and income elasticities).
- Greater utilization of biosimilars and generics as less expensive substitutes, meaning that a severe recession will trigger faster and greater adoption of biosimilars and generics.
- Lower utilization of drugs in therapy classes where patients must absorb a proportionally greater out-of-pocket expense.
- Lower drug compliance (the filling of a prescription received from a physician) and adherence (how patients take their medications). For example, patients spreading daily medication usage over two days.
- Greater utilization of mail order relative to retail pharmacy as a channel to receive medications at a lower cost.
- Greater physician demand for samples, especially in geographic areas or population segments that are more sensitive to changes in economic conditions.
- Greater demand for enrollment in company patient-

"Is the US pharma industry prepared for another recession? The best educated guess from this author and economist: No!"

assistance programs to offset the effects of losing drug coverage and affordability/access issues due to lower income from unemployment.
- Patients with multiple conditions in difficult economic straits will more likely choose continuing drug therapy for symptomatic conditions over asymptomatic ones. Thus, for example, older individuals who have osteoarthritis, diabetes, and hypertension will more likely choose continuing their osteoarthritis medication over the latter conditions, even though controlling their diabetes and hypertension is likely more medically important. In short, patients may make suboptimal healthcare choices.
- Greater movement by patients into catastrophic higher deductible health plans, as they are less expensive but will also translate into receiving fewer medications given the higher out-of-pocket expense. Less access to healthcare and drugs will have adverse consequences on health outcomes and overall medical care spending.
- Greater geographic variations in drug demand utilization seen around the world as the recession could generate different local and regional effects. For example, during the Great Recession, specific cities and regions in the US that relied more on heavy manufacturing and auto production for their economic base (like Detroit and "rust-belt" states) were severely impacted. Greater drug demand effects would be seen in local areas and regional economies that were less economically diversified and more susceptible to any one change in a recession index.

Datasets exist that capture all the above relationships which in turn can be empirically measured using various econometric models to support sales/marketing/payer tactics.

Preparing for the worst

"What we know about the global financial crisis is that we don't know very much." Paul A. Samuelson, Nobel Prize-winning economist.

Is the US pharma industry prepared for another recession? The best educated guess from this author and economist: "No!" Pharma commercial organizations, by their nature, presume management control variables, such as sales, marketing, and contracting efforts, directly affect prescription volume to the exclusion of external factors. They are not looking at macroeconomic effects on prescription sales, nor do they have the modeling expertise and experience in analyzing such effects. In addition, as macroeconomic conditions are beyond the impact of individual companies, the view may be that their effect on prescription volume is not something that needs be considered in the business planning process. Such a view is incorrect. Though macroeconomic conditions are exogenous factors to be treated as a given by companies, it is important to know the effects of such trends on prescription volume and other key outcomes – and what can be done to mitigate those effects.

Given the typical risks and uncertainties of making future forecasts, there are a number of precautions that pharma companies can take to prepare for the effects of another recession.

- Predict when a recession will start. Admittedly, such predictions are challenging! However, an array of forecasts exists from governmental institutions, private sources, and academic organizations. Waiting for an official proclamation that a recession exists is a far worse scenario. The measurement that a recession exists essentially means that at least two consecutive quarters of an economic downturn have occurred. Waiting for the official announcement means at least a half-year has already passed, meaning the effects from a recession have had time to affect patients and other healthcare system stakeholders (which may not be reversible), and less time for business plans to be enacted to help mitigate the effect.
- Estimate the severity. Assessing severity will help determine the amount and type (sales, marketing, or managed markets) of resources that need to be deployed to mitigate recession effects.
- Determine how long it will last. From a business planning standpoint, you need to know how long resources must be devoted to mitigating recession effects at the brand level.
- Assess the differential effects. The Great Recession had differential effects by geography, industrial sector, and socio-demographics. And the next one will, too.
- Prepare contingency plans that can be put in place at the first sign of a recession. Pharma companies have a number of processes where the risks and effects of a recession to the business can be incorporated into future plans. First, brands go through quarterly and annual business reviews that assess both strategic and tactical plans. Second, prescription and financial forecasts are developed based on market and environmental trends. These forecasts can easily incorporate

There is good reason to believe that the next recession may be just as severe as the last Great Recession.

- Global and US consumer debts are at record levels (1, 2), which means governments and consumers (i.e., patients) will be in more leveraged positions when a recession occurs and thus unable to sustain spending, including on pharmaceuticals and healthcare.
- US federal government annual budget deficits will reach $1 trillion in 2020. Total receipts and outlays were reported for the first nine months of the fiscal year 2019. Increases in entitlement spending, especially Social Security and Medicare, will continue to rise as the baby-boomers enter these programs. These structural deficits are unsustainable and place upward pressures on the real cost of capital (interest rate), thus further increasing the cost of financing these deficits. Worse, political parties seem unwilling to make hard choices about tackling our deficit problem, viewed as mainly a spending issue as noted by the final report from President Obama's bipartisan National Commission on Fiscal Responsibility and Reform (also known as Bowles-Simpson) (4). The budget agreement for 2020 and 2021 not only demonstrates an unwillingness by political leaders to address the problem of long-term structural deficits, but also unfortunately adds to them (5).
- The global economy is showing signs of weakness: a) significantly lower GDP growth in China (in large part caused by current trade conflicts with the US), b) slower growth in Europe (including risks about a no-deal Brexit), c) numerous geopolitical hotspots around the world that are creating an environment of uncertainty, and d) high leverage risks in emerging markets, which taken all together raise concerns that the foundations for the next Great Recession are coming together (6, 7, 8, 9).

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"Models and analytics can help design and implement plans to mitigate any effects from a recession on physician, patient, and payer behavior."

recession risks at the national level, but more importantly at the metropolitan area, especially for the top local markets key to brand success. Third, companies generally create a "risk register" or a list of future potential events that could occur (along with their likelihood of occurrence, severity of business impact, and rating of business importance or priority) that could affect business operations. The occurrence of a recession could be included on this list of potential future events that place the company at risk.

Implications for US pharma

One key difference between the Great Recession and any future recession relating to pharmaceutical demand is the availability of health insurance that is now detached from employment through market exchanges via the ACA, which was not previously in existence; in theory, people do not have to lose their coverage when they lose their job. However, if the insurance is too expensive, people facing economic hardships will likely drop coverage, significantly raising the out-of-pocket drug costs, thereby decreasing patented drug demand and patient adherence. Moreover, much of the health insurance coverage expansion was for Medicaid, which for pharma companies is low-margin business and where plans generally have strong biosimilar and generic preferences. Also, the repeal of the ACA mandate and financial penalty has likely contributed to a rollback of healthcare coverage, making people and, thus, drug demand more susceptible to an economic recession. Lastly, people may choose to change the quality of their health plan, from more comprehensive and lower deductible/co-pay coverage to essentially a catastrophic plan but with poor coverage and higher out-of-pocket expenses when it comes to general health and drug maintenance and coverage to reduce premium costs.

We can therefore draw the following conclusions about the next recession and its effect on the US pharma industry:

- Signs are building for a recession in the near future – potentially 2020 – according to recently surveyed economists and uncertainties concerning global economic/geopolitical conditions.
- Many signs point to a potentially deeper recession than the Great Recession of 2007–2009 given structural economic problems, slower growth outside the US, international trade issues between the world's largest trading partners, and geopolitical risks/uncertainties.
- The pharma industry's shift to expensive specialty medicines, coupled with payer costs shifting to patients, means drug demand is increasing in recession sensitivity.
- The ACA will likely do little to help patients pay for medicines and will not mitigate the negative effects on drug demand when a deep recession occurs.
- Issues with government debt (also seen in many countries worldwide) will mean added economic constraints by the public sector against spending increases to maintain healthcare and drug services. Such constraints will likely result in increasing controls in the US and beyond against patented biologics and branded drug utilization and spending, and favoring substitution to biosimilars and generics.
- Pharma companies are likely unprepared. They may not currently have the analytics or processes in place to predict recessionary effects on drug demand or know how to implement changes in sales, marketing, and payer tactics.

The important relationships that hold the key to understanding the full effects of a recession on drug demand (and the resulting impacts) can be predicted, estimated, and assessed prior to the actual event. Models and analytics can help design and implement plans to mitigate any effects from a recession on physician, patient, and payer behavior.

Alleviating adverse effects

What role should company commercial analytics have in mitigating recession-induced drug demand effects? There is a wealth of historical economic data that already exist, while economic forecasting companies project forward trends on the types of measures that would trigger recession-induced drug demand effects. Econometric inference models – developed at the

local or regional level – can help determine the extent of drug demand effects from changes in specific economic factors relative to company management control and market-oriented variables (sales, marketing, and market access). Empirical results would reveal variations by geography in these relative effects given the wide diversity of economic conditions. Results from inference models could then be used to estimate future drug demand effects based on projections of economic activity and assumptions on company management control variables going forward.

There are numerous potential business insights gained from the previously stated research path of applying commercial analytics in combination with econometric inferential and prediction models to economic and non-economic data on drug demand. For example:

- The results may reveal surprising insights that economic trends play a much more significant role in affecting drug demand relative to management control variables than first thought. Given the growing trend toward launching expensive specialty medicines, the structure of economic variables is likely to play an even greater impact on drug demand relative to traditional sales and marketing channels. Marginal, elasticity, and relative importance (standardized coefficients) estimates could be derived from a wide range of drug demand models.
- A company can position commercial resources differently by local area according to economic dynamics. Local/regional differences in economic effects may suggest variations in managed care contracting, demonstration of greater drug value through promoting disease management programs, differentials in drug messaging through personal/non-personal/consumer promotion channels, and so on.
- National, regional, and key local area company financial forecast accuracy could be improved by introducing the effects from economic variables, which could determine the extent of any drag on financial forecasts from recessionary effects.
- Models could be used to determine not only specific drug demand by prescription type, but also by payer channel and brand to generic substitution ratios. One would expect that, as a recession becomes more severe and lasts longer, forecasts could be developed to see how many prescriptions move from third-party commercial to Medicaid, or from retail to mail order.
- More advanced modeling can be developed to measure the negative effects of a recession on drug utilization and adherence on patient health and economic outcomes. The reason for this connection is due to an increasing prevalence of performance-based contracts between pharma companies and payers/pharmacy benefit managers (PBMs). Recent published evidence looking at Detroit revealed that the Great Recession reduced overall population health (25). Making such connections in real time will require the use of patient-level claims data and electronic health records, along with applications of artificial intelligence and machine learning. Pharma companies can also understand more fully the effects of co-pay offset programs to mitigate recessionary effects on health and economic outcomes.
- Pharma companies can use artificial intelligence and machine learning to predict which patient segments per drug will have more affordability problems paying for medicines during a deep recession. Such algorithms can also be used to predict enrollment applications in patient assistance programs. Algorithms can initiate the next best action towards locality based on the predicted effects of changes in economic conditions.
- Analysis could estimate differences in the price elasticity of demand for different drugs by geographic regions that see variations in economic distress. Such analysis will also likely pick up differences in drug price elasticities for certain life-threatening and rare conditions versus other conditions; similarly, we should see differences between symptomatic versus asymptomatic health conditions.

In short, another recession is highly probable. Companies need to be aware of the full extent of the potential impact. Management control should be exercised now to mitigate adverse effects.

George A. Chressanthis is Principal Scientist at Axtria, USA. George has almost 25 years of pharmaceutical industry knowledge and experience gained through working within companies advising senior executive teams, functioning as an outside consultant, and conducting research as an academic. He also holds a Ph.D. in economics from Purdue University and earned a full professorship in economics with tenure and graduate faculty status at Mississippi State University prior to his pharmaceutical career.

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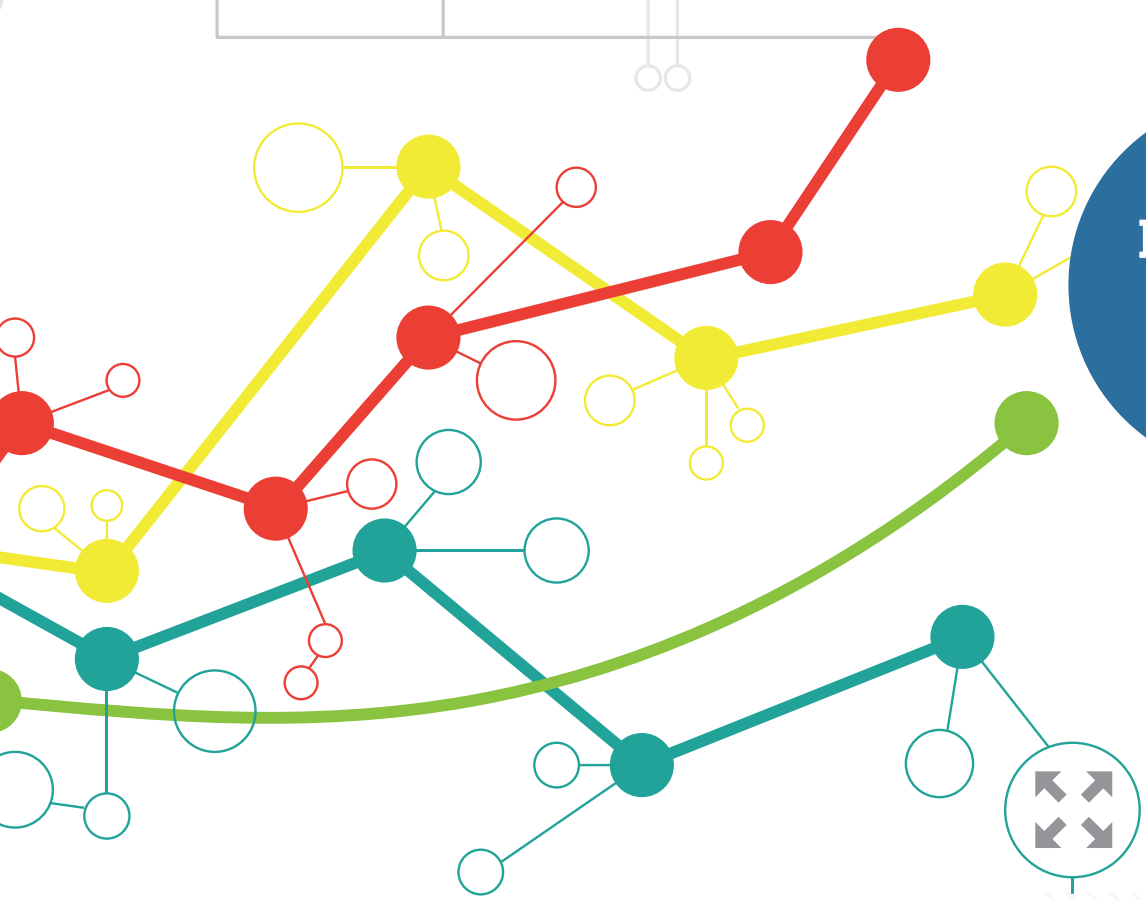


NextGen

R&D pipeline
New technology
Future trends

Meet "Molecule" – the Pharma Development Disruptor

Open source platforms have transformed software development and led to lower costs for consumers. What would happen if pharmaceutical R&D applied a similar approach?

With Paul Kohlhaas, founder of Molecule

Blockchain technology in the pharma industry is commonly associated with supply chain management, but the technology can be used in other ways to benefit drug developers. At my not-for-profit company, Molecule, we have developed a platform using blockchain technology to create a more collaborative approach for drug development. I like to describe Molecule as a platform that offers an open market for intellectual property, where researchers, companies or investors can acquire shares in a molecule and/or work on the molecule to contribute to its development.

Learning from the software giants

The Molecule platform was born in 2018. The idea was to align all the stakeholders of the drug development pathway – including the academic institutes and small biotechs that provide intellectual property and groundbreaking research, pharmaceutical companies, consumers, investors, or even regulators – in a more collaborative-based marketplace for drug development.

The approach is deliberately open source – the same kind of system that is used in the development of software (particularly for computer operating systems). Open source has had an impact on the relative speed and cost with which new software is introduced to the market, and many of the software giants today have moved into the open source community; the Microsoft loves Linux mantra, IBM's acquisition of Red Hat, Oracle cultivating the open source Java platform and language, are just some examples. Open source helps to reduce the costs of developing new software. Consider Microsoft as an example; in the early 1990s, Microsoft was developing software in house, using only Microsoft resources. Development costs were significantly higher than the actual cost required to manufacture the software discs, and the development costs were passed on to the consumer which, along with the fear of the growing global dominance of Microsoft, led to the establishment of Linux, which offered free, open source software that would run on personal computers.

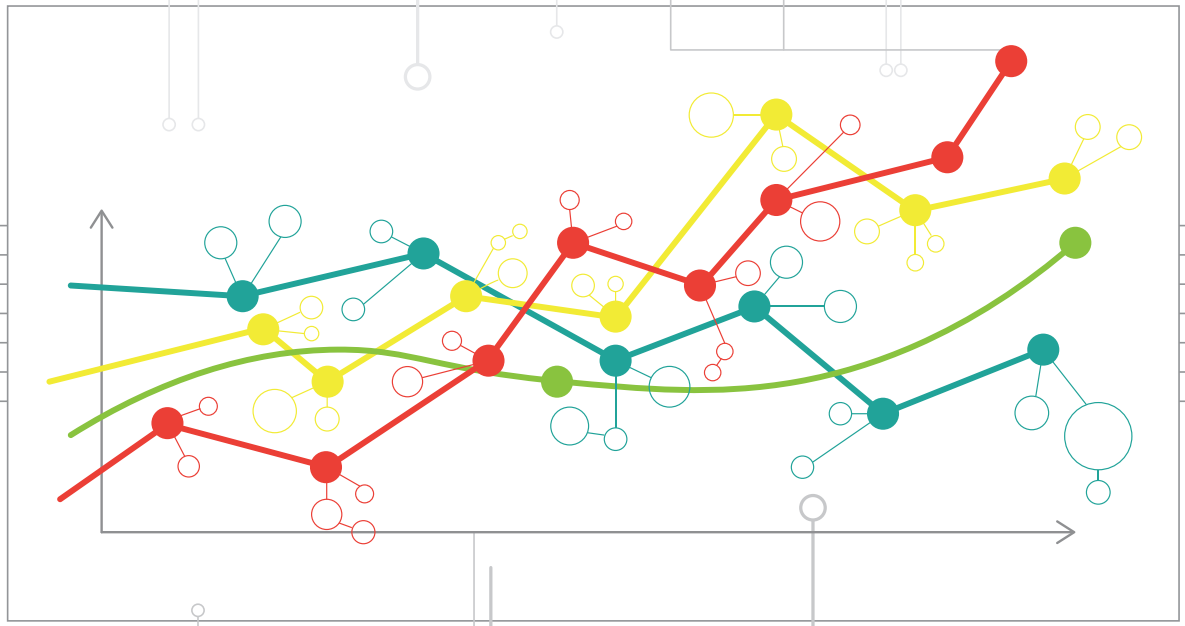
Let's compare this to the pharmaceutical industry. The development of a new prescription medicine is estimated to cost around $2.6 billion. Manufacturing costs are generally only a small percentage of the overall cost of development, so the high costs of medicines handed to the patient or through reimbursement are a reflection of the development costs (and failures along the way) – just like Microsoft software in the 1990s. Moreover, just as Microsoft used to do all of its development in house, the pharma industry also keeps its R&D in house and behind closed doors.

The open market

For pharmaceutical companies, patents are very important, but have ultimately instilled a culture of secrecy. Many companies fund entire R&D empires to ensure all data captured (good and bad) is retained in-house and kept as private property. This lack of open dissemination of experimental results ultimately stymies the advancement of the processes and sciences fundamental to R&D. Negative results aren't published so mistakes and failures are reproduced across the industry, contributing to the escalating costs of development across the industry.

A patent allows one company to monetize all of the future commercial profits that could be derived from a new drug – and anyone else trying to research that drug could be sued. As development of a product proceeds, more money is spent, but as milestones are passed, the likelihood of success increases. This adds value, progressively, to the patent and is often the basis for growth in the enterprise value of a biotech company as it continually raises and spends investor money to develop an asset. With Molecule, we take the original patent, ideally at the very early stages of its life, break up its ownership into saleable units and offer them on a market to create a new commodity

"Negative results aren't published so mistakes and failures are reproduced across the industry, contributing to the escalating costs of development across the industry."



The Man Behind Molecule

My academic background is primarily in economics and politics, but I became interested in how the pharmaceutical industry worked during high school. I had some friends who were personally affected by the over prescribing of medication (and other issues), which led to me wanting to understand the underlying drivers of drug development – and how it was causing problems for patients. Today, market dynamics within the industry are still problematic; for example, there is the opiate crisis in the USA, but then, on the other hand, there are many situations where patients cannot access important medicines because of cost.

As well as being interested in pharma, I've also always been fascinated by technology. During my university years, I was introduced to Bitcoin, and I started to examine some of the infrastructure behind it, including blockchain technology. One of the main benefits of blockchain is decentralization – and I wondered if this technology could be used to promote change in pharma by creating a decentralized approach to developing drugs – one that distributes cost, risk and ownership of molecule.

The Benefits

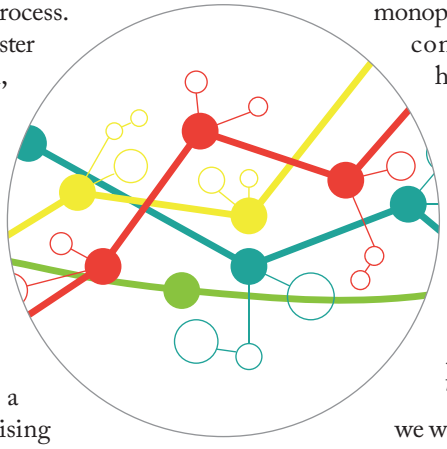
- Pharma and biotech companies can list their assets in various development stages, securely share R&D data and access financing and collaboration partners.
- Universities and scientists can contribute openly to other IP assets in exchange for a stake, open up their discoveries and finance early-stage IP development.
- Patients and Investors can direct capital and attention into the most promising cures, crowdfund their development and accelerate clinical trials.
- Contract research organizations can discover IP in their area of expertise to work on, accessing automated payment, data and IP sharing infrastructure.

that people can invest in – and which can fluctuate like any stock or share. Moreover, we now have something that promotes openness and transparency in drug development as any "news" or new research findings will impact the value of the patent and the value of the individual units.

The incentive model described above will be familiar to investors, but for pharmaceutical R&D it's important to not only tap into finance, but also scientific expertise. By purchasing some shares in a patent, a researcher would have part ownership of a molecule, which may, in the future, bring financial reward but immediately gives the researcher access to data and the right to work on the molecule and publish the results openly, as an academic researcher would. This additional research brings "news" to the shareholders, possibly affects the pricing, and, importantly, shares any and all data openly with the world. Now we have pharmaceutical development out in the open and free!

There are many experimental drugs at various stages of development, from concept to clinical trial, and further progress is dependent upon priorities set currently by industry – time to market, market size, efficiency, cost of investment, resources, and so on. In our new marketplace, a patient can see what is in the pipeline and back the programs they wish to support – perhaps to help bring a new specific type or category of drug to the market – as opposed to buying shares in a pharma company that can choose at any point to drop the program. Ownership and a direct connection will inevitably help drive a patent forward.

In providing an open platform for all, we should see patents, programs and drugs supported by a wider variety of people, institutions and perhaps even patient support groups at different stages of the development and commercialization process. Such a platform will foster better collaboration, openness and a different culture alongside new incentives and an alternate method of financing.



On Molecule, raising financing for the development of an asset works in a similar fashion as raising financing for a company. An IP asset, or bundle, is fractionalized into shares and then distributed between multiple parties in exchange for funding or work on the compound. This can go through several rounds of financing until the market is fully opened, or can be opened early on. The mechanics of how much financing is raised, retained in the market and distributed is highly dependent on the specific use case and stage of the assets development.

Disruptive ambition

In launching any ambitious project, it is better to start focused and branch out as the initial momentum takes you forward. For Molecule, we are beginning by marketing this service to a select number of disease areas where we feel our approach offers a distinct advantage.

We decided to focus on a few key areas of research with our launch. These are:

1. psychedelic studies
2. aging and longevity
3. rare and neglected disease

These are areas where there have been exciting developments recently, but there is a need for funding. These are also areas that we feel would directly benefit from broadly-owned IP to prevent monopolization by a single company. We have a handful of projects from these core areas of focus that are extremely exciting, and we cannot wait to announce them! They will launch in series shortly after the first project is live.

The second project we will be launching deals directly with the search for a molecule that could have a positive impact on longevity and healthspan (as well as lifespan). A lot of exciting preliminary work has been performed

already, and we believe the broader biogerontology and longevity communities will be excited to hear about the project. Interestingly, there is a lot of crossover between the crypto, psychedelics, and longevity spaces. We hope to work to increase the cross-pollination of ideas in these areas with Molecule.

The rare and neglected disease spaces are always in need of funding. We believe we can help assist in areas where strong commercial interests don't exist by creating models for therapeutics for rare and neglected diseases. We are also putting a strong focus on early stage IP from small to mid-sized biotech companies, with the aim of attracting funding for particular programs rather than having to raise company-wide equity finance. However, we also don't want to forget universities, particularly those wishing to adopt open innovation culture, where IP is continually being generated and in need of progressing. Here, there is a wealth of opportunity for early stage IP, collaboration and commercialization – and our approach gives universities an alternative to either forming a traditional spin off or licensing technology early, which can result in lost research access and future revenues.

Molecule will be going live soon. We have a number of companies in the process of subscribing, and a pipeline of early adopters through our soft launch. During development, we've done a lot of research into the legal aspects of patent ownership. Patent law is very complex and constantly evolving – and we still have questions to answer – but given that Molecule is about transparency, there will be clarity for all shareholders.

For the time being in phase one of our project rollout, we are not working with patents in our initial alpha, and will slowly begin working with patents and IP once we enter into our beta. Initially, we are focusing solely on the development of our tech stack and looking at what kind of activities we can coordinate without IP playing a role. As some of these technologies are relatively new and untested, we want to understand how they can be used in a meaningful way before beginning to work with high risk asset classes.

"In our new marketplace, a patient can see what is in the pipeline and back the programs they wish to support."

We will introduce patents onto our system slowly and carefully, as this is a complex space and we want to ensure that we can distribute ownership in IP across jurisdictions without creating too many issues or encountering road blocks. However, there is still a lot of work to be done. This is where high quality legal guidance and leadership becomes extremely important.

Due diligence is also an important part of the evaluation process of a project for us. We use a 100-point rubric grading metric for the early analysis of the viability of specific projects we look at conducted by our Scientific Lead, followed up by an evaluation from the broader team, which includes external experts from a variety of backgrounds.Projects must meet some key criteria, such as the raise amount, the project being able to be carried out in multiple phases, and providing sufficient background evidence to support their thinking and hypothesis. We are refining this process as we dig deeper and engage more with researchers to understand their specific needs.

We realise that the success of our early projects is going to be instrumental, and thus have been working to develop evaluation criteria to be able to determine the likelihood that a project will be successful in achieving its core goals.

Culture shock

The biggest fundamental challenge of this model will be bringing about the culture change required for people to comfortably adopt open innovation in its full sense. Can drug development data be made truly open and accessible? What impact will this have on the perceived value of the time-honored hidden data culture, know-how or even trade secrets? We need to promote the benefits of the system, the accessibility, knowledge-sharing, and even go as far as reminding people the value of sharing negative data. If we can prove that our model works for collaboration, accelerating discovery and, perhaps most importantly, economic reasons (in terms of both access to working capital and eventual up-side returns), we anticipate broad adoption.

I hope our model will become disruptive to the current pharmaceutical culture. We are intentionally exposing the scientific research that underpins new medicines, making this accessible, and providing a space that is easy to interact with and that gives everyone a chance to become involved. The platform may, one day, devalue our current reliance on patent-centric systems, but we hope we will allow a better approach to open innovation and collaboration, both reducing the cost and time it takes to bring new drugs to the patients who so desperately need them.

Breathing Easy

Recent years have seen renewed interest in inhaled drug delivery. We take a deep dive into inhaled formulations with Lei Mao, Director of Inhalation Science and Product Development at Recipharm Laboratories

What was your route into inhaled drug development? And why is this such a fascinating field?

When I started my career as an inhalation formulation section head at Norton Healthcare in the UK (which later became IVAX, UK, and is now part of Teva), I was fortunate enough to work with colleagues who developed Spinhaler, the first commercially successful dry powder inhaler (DPI). During that time, I learnt that DPI formulations are counterintuitively the "simplest" yet "most complicated" among all dosage forms. On the one hand, DPI formulations only contain two ingredients: micronized API and lactose – and it doesn't get much simpler than that. (My colleagues used to joke that the first DPI formulation was prepared in the laboratory by shaking the ingredients in a plastic bag!) On the other hand, you must achieve good product performance from a fixed device with only two components – and that it is extremely challenging. This melding of simplicity and complexity really drew me to the field.

Since starting my career, I've been fortunate to witness constant advances in inhalation science, along with the launch of many patient-centric products. Asthma and chronic obstructive pulmonary disease (COPD) are two of the most prevalent diseases worldwide – most people will know someone who suffers (or suffer themselves). I've had colleagues who suffered with asthma and the inhaler significantly improved the quality of their life. And that really emphasized to me the importance of my field of work.

How has the inhalation field evolved over the years?

Inhalation as a method of delivering drugs has a long history in medicine, going back thousands of years to when medicinal herbs were burnt to ward off disease. Around the 1860s, the first nebulizer designs were introduced, one of which (using the venturi principle) remains in use today. However, inhalation therapy was not widely accepted until the mid-1950s, when Medihaler-Ept (epinephrine) and Medihaler-Iso (isoprenaline) – the first versions of metered dose inhalers (MDIs) – were launched, changing the lives of asthmatic patients forever. They were often referred to as "rescue inhalers." Since then, many other inhalation delivery devices have been developed and launched; for example, Spinhaler, the first DPI (launched in late 1960) and Respimat, the first soft mist inhaler (launched in 2011). Today, there are numerous devices on the market, which fall within four main categories – MDIs, DPIs, nebulizers, and soft mist inhalers.

Remarkable progress has been made in recent years, including advances in device technology, improvements in container closure systems, a move towards more environmentally friendly propellants, new excipients, advances in particle engineering technology, and smart add-on devices. All of these innovations have been aimed at improving inhalation delivery efficiency, clinical efficacy, patient compliance, easy disease management, and environmental sensitivity. In my view, these are the main areas that inhalation scientists will continue to focus on in the near future.

One area where there is certainly room for improvement, however, is in the cost of inhalers. When the CFC metered dose inhaler (MDI) was phased out, we witnessed a sudden surge in price, increasing to almost $50 in the US – even with insurance. I think it is very important for companies to make inhalers more affordable for patients, by supporting the development of new products and generic alternatives.

When is inhalation the preferred drug delivery method?

Respiratory diseases will remain the main target for inhalation therapy given the need to achieve a rapid onset of action through direct delivery to the lungs. According to Global Initiative for Asthma and Global Initiative for COPD, the estimated global patient population is over 300 million. For these diseases, there is no effective "cure," so we must alleviate, control and manage the disease. The standard protocol is to diagnose from symptoms, prescribe medication to assert control, adjust/reduce the doses accordingly when the symptoms are under control, and monitor the dose administration over the long term.

In addition to respiratory diseases, we have also seen continuous interest in delivering medicines for systemic therapy via the lungs because of the advantages of rapid absorption and higher bioavailability. This is essentially because of the large alveolar

surface area, thin epithelium, abundant blood circulation and low enzymic metabolisms. These medicines include peptides and proteins such as insulin, vaccines and more recently SiRNA, as well as some severe pain relievers. Non-invasive, self-administration and rapid onset are the main drivers for inhalation as an alternative to other dosage form such as injection.

What are the biggest technical challenges involved in developing an inhalation product?

Developing an inhalation product requires multiple disciplines, including device, particle and formulation technologies, aerosol and manufacturing sciences, and regulatory expertise – and because of the extent of the challenges, outsourcing is often preferred. Inhalation product performance and quality are

"One area where there is certainly room for improvement, however, is in the cost of inhalers."

determined by the combination effects from both formulation and device; therefore, regulators consider inhalation dosage forms as a combination product.

The majority of marketed DPIs use micronized drugs and carrier lactose blend as formulations, and understanding the interaction between the two, as well as how to modulate the interaction force through selection of the physically stable micronized drugs, are the main tasks for DPI formulators.

The production of inhalable particles is another key challenge. Inhalation drugs require free-flowing particles with even morphology and surface properties for best performance. The main particle engineering technologies used are spray drying, supercritical fluid processing, and controlled crystallization.

Spray drying has been successfully used to produce inhalable particles, especially the labile peptides and proteins, whose chemical stability is retained due to the amorphous or glass structure of the spray dried particles. The disadvantage of amorphous spray dried particles is their hygroscopic nature, which demands stringent environmental conditions; products must be protected from moisture throughout the entire manufacturing process, from particle engineering to primary packaging.

Supercritical fluid processing produces crystalline particles with uniform particle size distribution and even crystalline surface, which benefits inhaled products in terms of both powder handling and aerosol performance. However, the scale-up process can be challenging.

In contrast to the micronization process, whereby large particles are broken into smaller ones within inhalable size range, controlled crystallization produces inhalable particles by controlling the process when the drug crystallizes from the saturated solution to assure even size distribution. Since the particle size is controlled while the seeds grow, the final particles have a crystalline surface, meaning they are less cohesive. The drug powders can be formed as a uniform formulation more easily and subsequently form better aerosols when delivered from the devices.

What are your top tips for a company embarking on an inhaled drug development program?

First of all, it's crucial to make evidence-based decisions early on to get the project started on the right tracks! Therapeutic application, target patient population, drug properties, doses, and dose regime all need to be considered when selecting the right inhalation dosage form and target product profile.

At a technical level, understanding the basics is the foundation for success in inhalation product development. Thoughts to keep in mind include:

- Inhalation development involves multiple steps, each with a sequential impact on later stage. Any technical issues must be fully understood and resolved as soon as possible – never ignore them.
- Using API as an example, ensure you understand and validate the micronization process and the properties of the input materials. You must be able to produce drug particles with consistent physical properties to ensure success. The impact of the process, as well as the impact of storage conditions post-micronzation, on particle size and distribution, crystallinity and surface morphology must be fully investigated and understood. Similarly, study and monitor the effect of the formulation and process, such as order of addition, homogenization and filling process, over the entire batch during early process development.
- A quality by design (QbD) approach is highly recommended.

"Inhalation drugs require free-flowing particles with even morphology and surface properties for best performance."

How do you expect inhalation therapy to further evolve?

Unmet patient needs and ongoing advances in science and technology are the growth engines behind inhalation therapy. In addition, there is an increasing interest in the fact that inhalation dosage forms can not only target local treatment, but also systematic delivery with rapid onset of action and potentially decreased adverse effects and increased bioavailability. These benefits could be used for therapeutics outside of the respiratory space.

From the delivery platform and formulation side, I see the need to continuously develop new technologies. A few examples include developing inhalation devices with better delivery efficiency, which are more compatible to the labile molecules, and the use of more environmentally friendly propellants. The field will continue to work on new production processes that will deliver better particle properties, more manageable formulations – and less complicated and better-controlled manufacturing overall. All of these drivers also work towards our wider ambition: to provide patients with the most effective, safe, and easy to use products.

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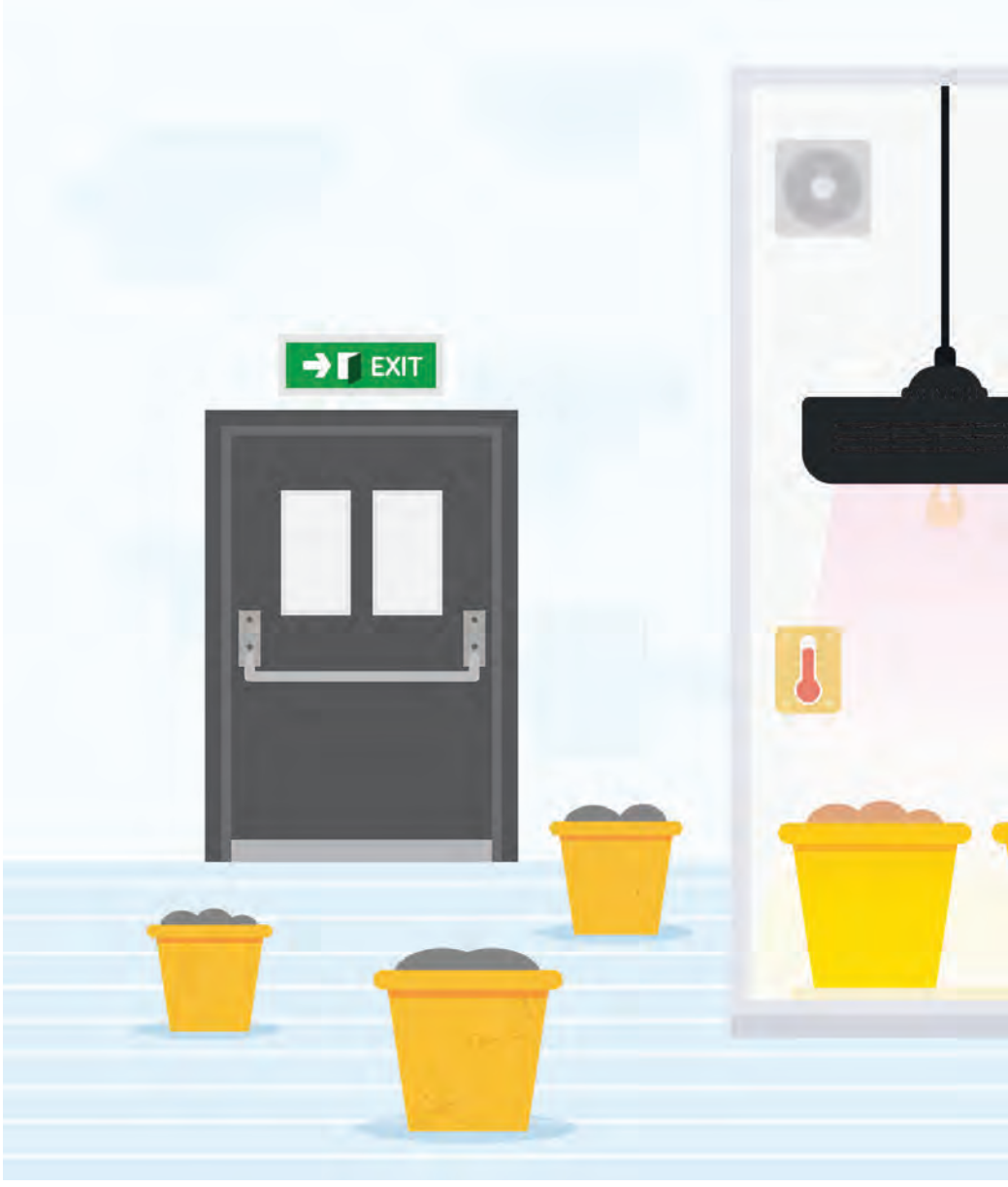
The Cannabinoid Factories of the Future

Cannabis plants produce hundreds of interesting compounds, but could microorganisms provide a more efficient means for their mass production?

By Matthew Hallam, Editor of The Analytical Scientist



Synthia (formally known as Mycoplasma laboratorium) was the prodigal child of synthetic biology – a living cell comprising the outer membrane of a hollowed-out Mycoplasma capricolum and a Mycoplasma mycoides genome synthesized completely from digitized sequence information (1). This science may sound more aligned with the plot of a Philip K. Dick novel than reality, but synthetic biology was pushing these boundaries as early as 2010.

Since then, researchers have extended the frontiers of this novel field. E. coli cells have been engineered with the ability to produce synthetic proteins from a genetic code containing manmade nucleotide bases – essentially re-sketching the blueprints of life – and we have also equipped living cells with computational capabilities, such as logic, memory and problem-solving. Though impressive, these breakthroughs tell us very little about what synthetic biology is – or what it has to offer in practical terms.

Simply put, synthetic biology is an interdisciplinary field that applies engineering principles to the construction of biological systems that fulfil prespecified functions (for example, the synthesis of fuels or vaccines) based on carefully designed genetic circuits. The gene editing approaches central to this field are adaptable, and are being harnessed to engineer microorganisms able to rival classical ways of providing commodities in many spheres.

In the medical cannabis industry, for example, microbes have been engineered with the capacity to produce a number of cannabis compounds – largely cannabinoids like CBD and cannabigerol (CBG), but also a number of further substances. Yet, these compounds represent only a fraction of the potentially therapeutic compounds found in the plant. In this sense (and others yet to be discussed), we have merely scratched the surface of synthetic biology's potential in this space.

The medical cannabis community has taken small steps towards a biosynthetic future – but what giant leap is needed before we usher in the age of cannabis' synthetic overlords? And why would we bother in the first place?

Biosynthetic superiority?

Thinking on the latter question of why, Anna Shlimak, Head of Investor Relations and Communications for Cronos Group, provided a clear rationale. "The potential uses of cannabinoids are vast, but the key to successfully bringing cannabinoid-based products to market lies in creating reliable, consistent, and scalable production capability across the full spectrum of cannabinoids."

"The medical cannabis community has taken small steps towards a biosynthetic future."

There are three basic ways to go about producing any compound at scale: synthetic chemistry, classical agriculture, or cellular agriculture (an umbrella term under which synthetic biology sits). When it comes to cannabis compounds, classical agriculture is clearly the historical method of choice, but the approach suffers from clear challenges. In fact, agricultural cultivation is burdened by a number of shortcomings.

"The agricultural approach is not economically effective or environmentally sustainable," says Jason Poulos, CEO of Librede Inc. "Hundred-thousand-foot greenhouses are needed to meet the demand for cannabinoids, which require not only colossal amounts of electricity to power, but also huge amounts of fertilizers and pesticides to produce a quality product." The negative effects of these compounds are widely documented, and span from depleting key insect populations to damaging human health and the environment.

"Producing these compounds in yeast, or another applicable microorganism, has the potential to reduce costs, stabilize the supply chain against issues such as weather variability, and increase accessibility," says Poulos. "In the case of molecules like CBD, an anti-epileptic medicine, accessibility should be our primary concern."

Crop growth is affected by many factors, and even slight perturbations can lead to changes in the yield of a target compound by 10 percent or more. In the interest of stabilizing supply chains and increasing accessibility, as Poulos suggests, we

The Biosynthesizers

Jay Keasling

A household name in the field of synthetic biology, Jay Keasling has spent 27 years at University of California, Berkeley, engineering microbes. The success stories in his portfolio? Biosynthesizing taxol (an anti-cancer drug) and artemisinin (an anti-malarial drug precursor), and an extensive number of biofuels. Keasling has also been involved in numerous business ventures, co-founding both Amyris and Lygos. The recipient of numerous awards in both bioengineering and innovation, Keasling says he is looking forward to focusing on increasingly elusive molecules as he embarks on future ventures including the biosynthesis of key cannabis compounds.

Anna Shlimak

Head of Investor Relations and Communications at Cronos Group – a global cannabinoid company committed to building disruptive intellectual property by advancing cannabis research and product development – Anna Shlimak plays a crucial role in communicating the company's cannabinoid biosynthesis programs. Working with Ginkgo Bioworks, they are making waves in the field of cannabinoid biosynthesis by using the expertise of both organizations to tackle key issues, such as scalability, access to rare cannabinoids and economic sustainability.

Jason Poulos

Librede is a company with a clear goal: to harness the therapeutic potential of nature. Cannabinoids represent valuable potential in this endeavor, providing a window of opportunity that CEO Jason Poulos was not prepared to miss. After obtaining his PhD in bioengineering from the University of California, Poulos wasted no time in immersing himself in the upper echelons of biotech business, soon developing the world's first yeast-based cannabinoid production platform alongside Anthony Farina. Today, his focus is on establishing a wide network of collaborators with whom to develop new methods for synthesizing molecules.

must be able to anticipate the amount of a compound obtainable from a given production process.

Accessibility is a key theme in biosynthetic discussions – but expanding the portfolio of medical compounds available through cannabis represents another important goal. Biosynthesis allows us to capitalize on promiscuous metabolic pathways (those able to process one of a number of substrates into different products) to produce unnatural analogues of target compounds; the cannabinoid pathway can produce many such analogues when fed variants of hexanoic acid.

Talking of these possibilities, Jay Keasling of the University of California, Berkeley, suggests that synthetic biology carries the major advantages of both synthetic chemical and biochemical manufacturing approaches in a single package. "The great thing about synthetic biology is that it provides a relatively simple route for producing natural molecules with stereochemical centers, and also facilitates the synthesis of molecular variants," he says. "This covers some of the weak points of synthetic chemistry and biochemical methods, respectively."

Rise of the biosynthesizers

With such advantages in mind, it should come as no surprise that big names across industry and academia are hoping to harness this untapped potential – our contributors included. For Shlimak, this is evidenced by Cronos Group's recent collaboration with Ginkgo Bioworks (a customized microbe design company); for Poulos, we need only look at Librede's history of biosynthetic cannabinoid patents; and for Keasling, recent success in synthesizing cannabinoids and their unnatural analogues in yeast speaks for itself (2).

Accordingly, Poulos highlights extreme levels of competition. "Every day there seems to be a new company wanting to enter this space. We're even seeing publicly traded companies take interest, but these groups quickly realize that saying is easier than doing," he says. Librede is developing a hefty patent portfolio to beat off competitors; the most recent of these covered an approach for producing THC acid (THCA) in yeast, with existing patents in place for methods concerned with the biosynthesis of CBD and CBG. The existence of so much competition so soon after changes to legislation points to rapid and continued progress for cannabinoid biosynthesis in the industrial sphere.

Feats elsewhere in academia also speak to

a rapidly advancing subfield. A team from TU Dortmund University (Germany) have engineered yeast with the ability to conduct whole-cell CBGA to THCA bioconversion (3), and, in August, Kevin Rea and colleagues from the University of Guelph (Canada) reported the successful biosynthesis of anti-inflammatories cannflavin A and B, also in yeast (4).

Keasling attributes these advances to a number of breakthroughs in molecular science, including DNA synthesis. Labs today are able to bypass cloning genes out of the cannabis plant completely, and can also alter the codons within to modify genetic expression as required. What's more, automation and robotics streamline the practical work itself, and dramatic advances in analytical technologies like mass spectrometry mean that we can analyze the biosynthesized products with high throughput.

With the aim of capitalizing on such advances to biosynthesize eight target cannabinoids, Cronos Group have recently purchased a state-of-the-art facility, which will operate as "Cronos Fermentation." Shlimak was happy to share a few details. "The facility includes fully equipped laboratories covering microbiology, organic and analytical chemistry, quality control and method development, as well as two large microbial fermentation areas with a combined production capacity of 102,000 liters. Plus, three downstream processing plants, and bulk product and packaging capabilities," she says.

Such facilities should provide the fermentation and manufacturing capabilities needed for Cronos Group to take full advantage of the work currently underway with Ginkgo. "Simply put, the process will be similar to that of yeast-based beer fermentation," says Shlimak, but current gaps in our knowledge of cannabinoid biosynthesis and the relevant technologies mean we have a way to go before upscaling to volumes as striking as 102,000 liters.

"The agricultural approach is not economically effective or environmentally sustainable."

Blockers to biosynthetic success

To upscale production, those in pursuit of cannabis compound biosynthesis must focus their expertise and ingenuity on three significant objectives: improving technology, reducing costs, and championing success stories.

Keasling believes that translating a biosynthetic cannabinoid product from laboratories to the market will be a crucial first step. "Getting a product into the market and placing it into the hands of consumers is essential because it will act as proof of concept to the public and evidence that this area of research was worth the investment," he says. Such success stories would likely then spur on further research; as Shlimak says, "Providing consistent and reliable products will facilitate additional innovation in this space by bringing new formats and technologies to the market."

A change in public perception would also help. The term genetically modified organism seems to incite confusion and fear even today, and an improved public understanding of its meaning would ease the movement of biosynthesized cannabinoids into the market.

In terms of improving technology, Poulos believes the field would benefit most from advances that focus on screening for the cannabinoids being biosynthesized, rather than on the genetic means for their production: "We can easily incorporate enzymes from countless organisms into a microbe of interest by simply printing the DNA encoding them. The problem is: how do we quickly test that the resulting cannabinoids are really there? It's not as simple as observing a change in color."

Poulos argues that such screening tools

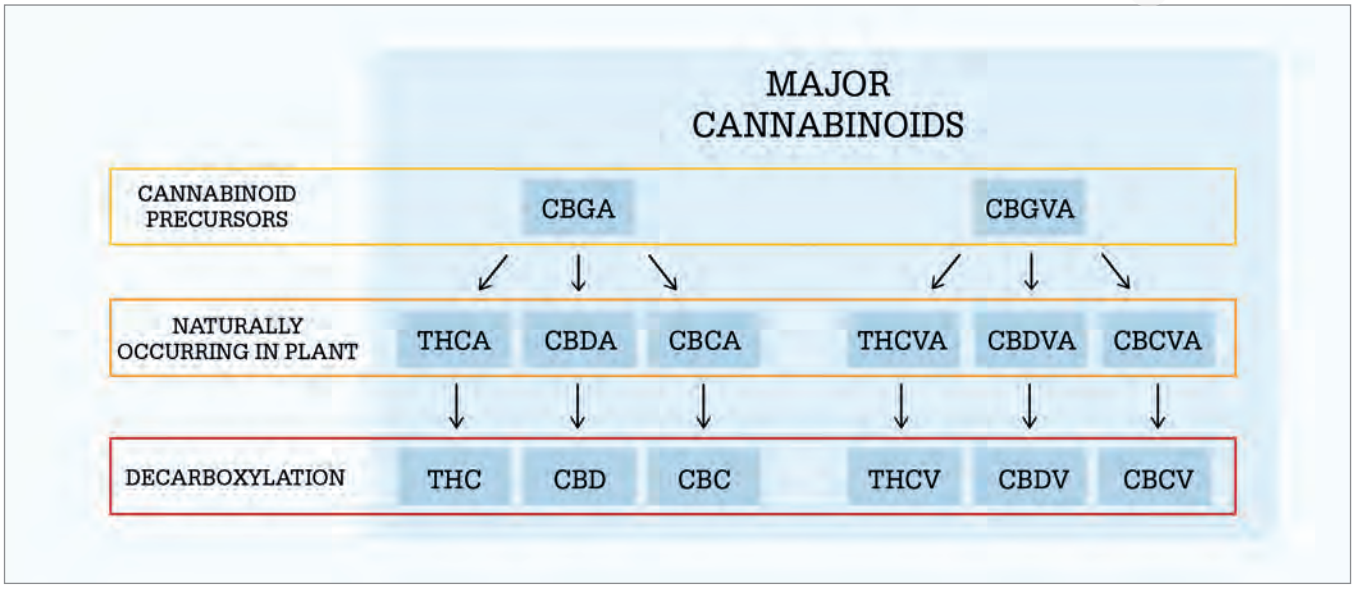


Figure 1. Cannabinoid metabolism in cannabis plants from CBGA and CBGVA "stem cell cannabinoids." Reproduced with permission from Cronos Group.

could be useful not just for cannabinoid biosynthesis, but also in biosynthetic efforts to produce classical pharmaceutical products, biofuels, and so on. "If I could snap my fingers tomorrow and have any breakthrough in this field in front of me, improved screening would be it," he says.

In addition, advances in the development of stable cell lines suitable for use on an industrial scale and downstream processing for cannabis compound extraction and purification are also needed. Low-cost materials will be central to these endeavors, which underscores perhaps the most important requirement for the field moving forward – reduced costs.

Though the chemical synthesis of cannabis compounds is incredibly expensive, costing around $40,000–70,000 per kilogram, Keasling suggests that costs as low as $100 per kilogram could be accomplished through microbial synthesis. With a wholesale price for CBD of around $5,000 per kilogram, reducing the price of biosynthesis represents a route to maximize yield and profit for the companies working in this space. Perhaps the most lucrative line of attack, however, will be the biosynthesis of lesser-known cannabis compounds with medical applications, which currently hold wholesale values of up to around $60,000 per kilogram.

Biosynthetic blockbusters of tomorrow

Cannabis compounds other than those typically mentioned in medical discussions are an important target for biosynthesis. Keasling refers to these as potential "blockbuster" compounds, and is excited to explore the utility of yeast to synthesize them. "I'm really interested in rare cannabinoids, but we don't know much about them because of the small quantities they're produced in. Yeast provides a great platform to further study these compounds, and I'm really excited to see these experiments unfold," he says.

These compounds also represent an important target for Cronos Group. "Our platform with Ginkgo will hopefully grant us access to cannabinoids present at low quantities in the plant, meaning that they are economically impractical, difficult or impossible to extract from agricultural sources. These could be medically important, and potentially very valuable," says Shlimak.

For Poulos, future ventures will focus on so-called "stem cell cannabinoids" CBGA and cannabigerovarinic acid – major cannabinoid precursors (see Figure 1 for an overview of their metabolism). Librede is already producing these compounds in quantities of hundreds of grams and is focusing on process improvements to lower costs. Next on their hit list: further compounds such as THC, CBD, cannabichromene, and tetrahydrocannabivarin.

Despite the potential and value of lesser-known and little-understood cannabinoids, the current drive of the field is clear. "From a pharmaceutical standpoint, the primary molecule of interest is CBD right now," says Poulos.

Beyond pharma, we should also expect to see applications for biosynthesized cannabinoids in nutraceuticals, beer, cosmetics, and any other markets that deem them useful. The demand for this research is clear – now it's up to researchers to continue pushing the boundaries.

Will we see cannabis greenhouses replaced completely by fermentation tanks? Maybe not anytime soon. But the case for cannabinoid biosynthesis – both in mass production and drug discovery – is certainly compelling.

Next-Generation Yeast

From bread to beer and fuel, yeast plays a key role in manufacture. Now cannabinoids join the list.

The cannabinoid biosynthesis race is as close as ever, and notable breakthroughs are popping up across all corners of the research world. Here, we take a deeper look at the method for biosynthesizing cannabinoids and their unnatural analogues in yeast from Jay Keasling's lab.

The team, led by lead author Xiaozhou Lou, engineered the native mevalonate pathway of Saccharoymyces cerevisiae (brewer's yeast) and introduced a hexanoyl-CoA pathway constructed from the genetic components of multiple bacterial species to achieve cannabinoid synthesis using a simple galactose substrate (1). Of course, genetic elements of the cannabis plant itself were also used – in particular, those encoding enzymes involved in olivetolic acid synthesis.

The researchers were also able to capitalize on promiscuous pathways to produce potentially useful compounds not found in the native plant. The team were also able to identify a previously uncharacterized enzyme and new genes encoding cannabinoid synthases during their efforts. "All the necessary pathway enzymes had supposedly been discovered, but we soon found that a previously documented prenyltransferase wouldn't work as needed partway through the study. This is a really critical step, and so we had to go back into the cannabis plant to find another," says Keasling.

The work represents an approach that could overcome many of the difficulties associated with pure chemical synthesis, including the high structural complexity of the molecules in question. The overall aim is to enhance healthcare for those who need it… But time will tell as to how these methods measure up against existing approaches.

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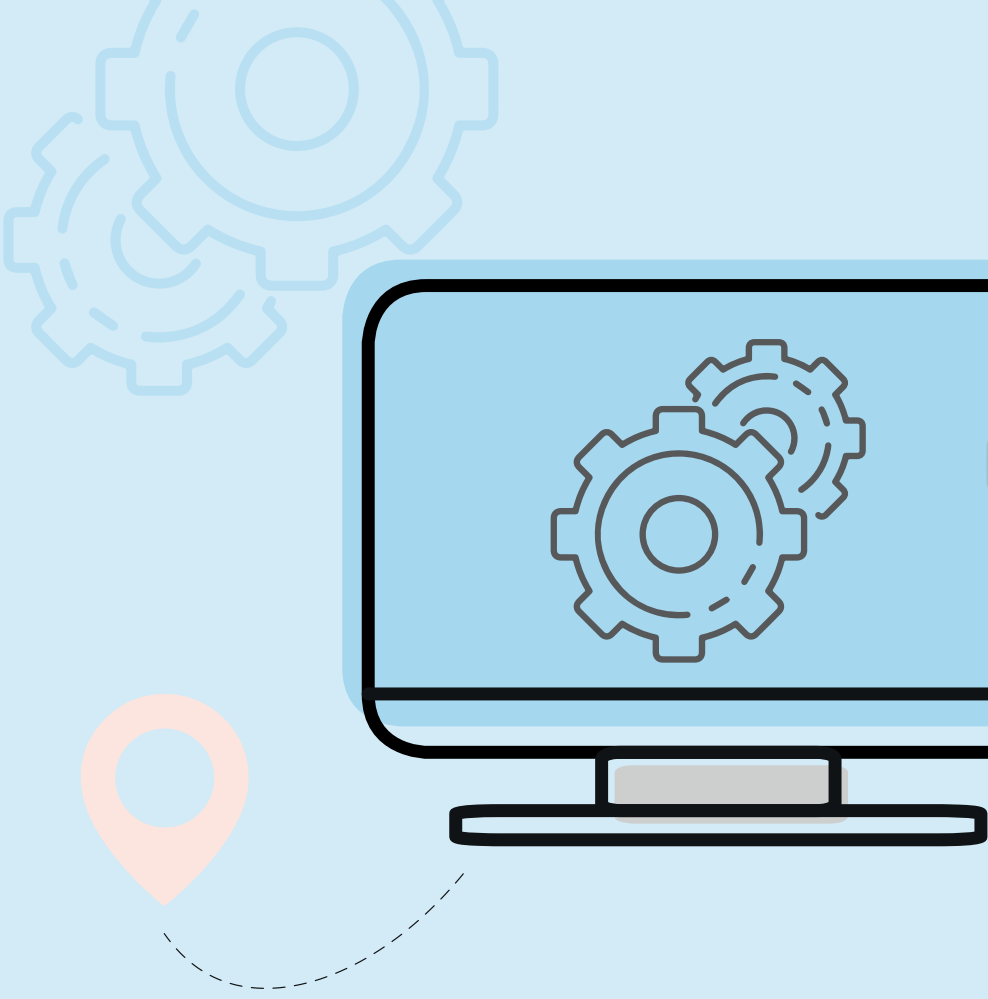
A Framework for Translation

Even the most promising research cannot benefit patients unless it can be guided down a successful pathway towards the clinic. Here, Andrew Davies, Professor of Haematological Oncology and Consultant Medical Oncologist at the University of Southampton, and Nigel Blackburn, Cancer Research UK's Director of Drug Development, discuss a partnership that focuses on one crucial aspect of that journey: early-phase clinical trials.



The translational journey, with Andrew Davies

Over the years, I've been involved in many aspects of early-stage and clinical research. My focus is on malignant lymphoma and the translation of novel therapies and relevant biomarkers into the clinic. To that end, I am the principal investigator on a number of early-phase clinical studies.

At the University of Southampton, UK, we've been conducting preclinical research into monoclonal antibody (mAb)-based cancer therapies for many years; in fact, the group has made several seminal observations in this field (1-4). Given our expertise, we were approached by a company called BioInvent, which has developed an mAb targeting the inhibitory FcγRIIB (CD32B) – a mediator of several immunotherapy resistance mechanisms. The mAb showed significant promise in preclinical studies, and so we worked together with BioInvent to submit a research proposal to the Centre for Drug Development (CDD) at Cancer Research UK; in brief, we had to explain the existing data and the rationale for taking the work further

– including unmet patient need.

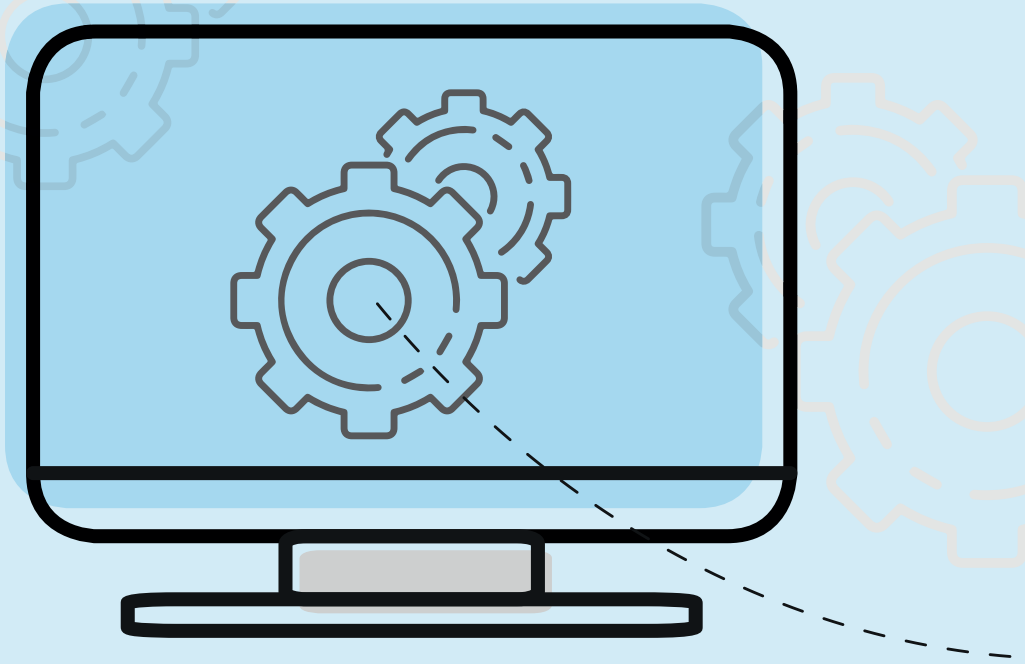
Now, working with the CDD, we have been able to generate the additional data required to open the clinical trial – as well as the capability and support to run a first-in-human (FIH) study. We really believe the CDD's significant experience in trial design, management, and strategy will help us deliver a successful project.

After we've defined the optimal dose of our single agent, which should not take too much longer, we will assess BioInvent's mAb in combination with rituximab (an anti-CD20 mAb). We hope we will see enhanced rituximab efficacy, given that blocking the CD32b receptor should prevent internalization of rituximab. We're really looking forward to moving onto that phase of the study. After all, if we can improve outcomes in those patients, it should open the door for us to assess this mAb in combination with a number of other agents; for example, immunomodulatory agents and chemotherapeutics. We have a lot of potential avenues to explore – it's an exciting time!

"When seeking innovation, first and foremost we are looking for patient benefit."

In terms of novel agents in blood cancers, there are exciting things coming from all directions. There is keen interest in the development of cellular therapies – chimeric antigen receptor T (CAR-T) cells and NK cells, which have tumor-targeting effects. We are now beginning to see the use of these in clinical practice. There are also exciting developmental lines in both solid and hematological malignancies, I think we will continue to see refinements in cellular therapies

"I love what I do and I think passion is vitally important. The field has a great deal of promise – especially for patients who don't have many options."



– despite complications in how they are delivered.

Among all these advances though, I remain particularly interested in the development of novel bi-specific antibodies that can not only engage the target antigen but also activate T cells. There are already results that demonstrate the efficacy of these agents (5) – and I believe such antibodies represent a more "off-the-shelf" solution than cellular therapies.

From an oncologist's perspective, we want to get much better at stratifying patients, so that we can take a more targeted approach to treatment. And so it's really exciting to be part of a research community that is moving towards this dream of delivering personalized therapies – all while enhancing our understanding of the biology of the disease we are treating.

The power of partnership, with Nigel Blackburn

As Director of Drug Development at Cancer Research UK, I oversee CDD, which has around 20 ongoing projects at various stages of development in its portfolio. What the CDD really brings to the table is a knowledge of how to take a potential new medicine from preclinical research through to Phase 2a clinical trials. We work with drug discovery scientists and chief investigators to collectively bring a molecule through FIH trials. Essentially, it is a partnership of complementary expertise.

In the example described by Andrew, we have also partnered with Bloodwise (the UK's leading blood cancer research charity) from a funding perspective. If the molecule makes it to market, both Cancer Research UK and Bloodwise will use any financial return to fund further research – the start of a virtuous cycle.

The work with BioInvent fits into a framework that we call a Clinical Development Partnership – something we employ for most of our pharma and biotech partners. In brief, we take a project – based on the partner's assets – through to proof of mechanism. At that point, the originating company has the opportunity to explore the data. If they like what they see, they can license it from us, and move the project onto the next stage themselves. We receive milestone payments as the project then moves through later development and marketing.

We've been involved in over 20

projects using this framework. For example, we've been working with a German biotech company, called Immatics, who exercised their option and have taken the molecule back in-house. There are several other companies who have done the same with molecules such as temozolomide (a mainstay of glioblastoma treatment) and Abiraterone (a prostate cancer treatment). Another example is Rucaparib (Rubraca) – a PARP inhibitor that was formulated and taken into human trials by the CDD.

The "dream" identified by Andrew fits beautifully with our efforts at the CDD. We are always on the lookout for potential new treatments. And when seeking innovation, first and foremost we are looking for patient benefit.

I'd like to close with an invitation: we're always happy to meet with both academics and biotech companies to discuss how we can work together.

To find out more, visit https://bit.ly/2CcR1oT

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Antibodies and Beyond

Sitting Down With…
Jane Osbourn, Chair at Mogrify and the UK BioIndustry Association, Cambridge, UK

Where did your career begin?

From a very young age, I've been driven by my desire to understand how the world around us works. I wanted to study something that really counted. I was a student and post-doc in the 1980s – PCR had just been invented and a revolution was taking place in molecular biology, so it was an exciting time to enter the field. Later, I switched my focus to the emerging area of antibody engineering and applied for a job at Cambridge Antibody Technology (CAT). The technical potential of human antibodies was tempting from an academic perspective, but as soon as I started working in a biotech environment, I realized the full extent of the applications in medicine.

What moments are you most proud of?

As a team effort, I was very proud of CAT. We spent a lot of the early years building large human repertoire antibody libraries, but our first real patient milestone for monoclonal antibodies was the discovery of Humira, which launched in 2002. We actually had patients come and talk to us about the impact that Humira had on their lives.

My recent OBE – order of the British Empire award – was also a defining moment.

I have been lucky enough to work with scores of very talented colleagues over the years, and my achievements always feel like a celebration of that teamwork.

What is your current focus?

Recently, I joined Mogrify. It's a great opportunity for me to apply my learnings from the biologic space to benefit cell therapy development. We are still in a very early phase of the company, with around 30 employees and all the programs are at the pre-clinical stage. Mogrify's technology can identify the optimal combination of transcription factors required to convert any cell type into any other cell type. We're now applying this technology to develop new therapies and address the challenges of efficacy, safety, and scalability of cell therapies.

"We must take an interest in why things failed – even celebrate failure – because we can learn from it and increase success rates."

I have also served as Chair of the UK BioIndustry Association (BIA) for the past four years. We've been doing a lot of work looking at the cell and gene therapy space in the UK. There are currently more cell and gene therapy developers in the UK than anywhere in Europe. The priority for the future is to find a way to go from autologous cell therapies to more universal systems. The UK has the right infrastructure for this, but there are big challenges in manufacturing. A number of the BIA's members are working in this space – looking at better delivery mechanisms, more consistency in cell production, and other solutions that should benefit manufacturing.

What changes would you like to see in the pharma industry?

There should be more focus on identifying drugs based on biological function first; we should be looking at how they interact with disease mechanisms, rather than specifically defined targets. The pharma industry is doing a really great job and has been hugely successful, but we are at a point where target supply in its classic form is becoming limited. We need to look at function first, and how to perform drug screening in a way that that will give insight into different areas of biology.

In addition, there are a lot of great leaders in pharma who think long-term and try to run ambitious long-term projects, but outcome measures in pharma tend to be more short-term because of annual budgets. Pharma needs to re-think how it is measuring success – considering five- or 10-year windows rather than annual goals. It is also important to reflect on success rates in the various stages of the discovery process. We must take an interest in why things failed – even celebrate failure – because we can learn from it and increase success rates.

What advice would you give to young researchers?

I didn't have a career plan – I followed my passion. My advice is to find your passion and really immerse yourself in it! Become an expert in something early on so that you go through the process of understanding how to get into a subject in depth. If you can do it once, then you will have the confidence to do it again and again in other areas. But wherever you are, keep asking yourself if you're enjoying it. I had a successful academic career, but I flourished in the biotech environment because there was a sense of pace, shared objectives, and ambition that I loved. I think it is very important to work out your ideal cultural environment and to keep checking that you are meeting your own goals in terms of satisfaction.

But at the end of the day, success in the pharma industry is all about collaboration. You must have the right collaborative attitude and make the most of other people's expertise in a mutual way. This is a theme that runs through my career – and will continue to do so.

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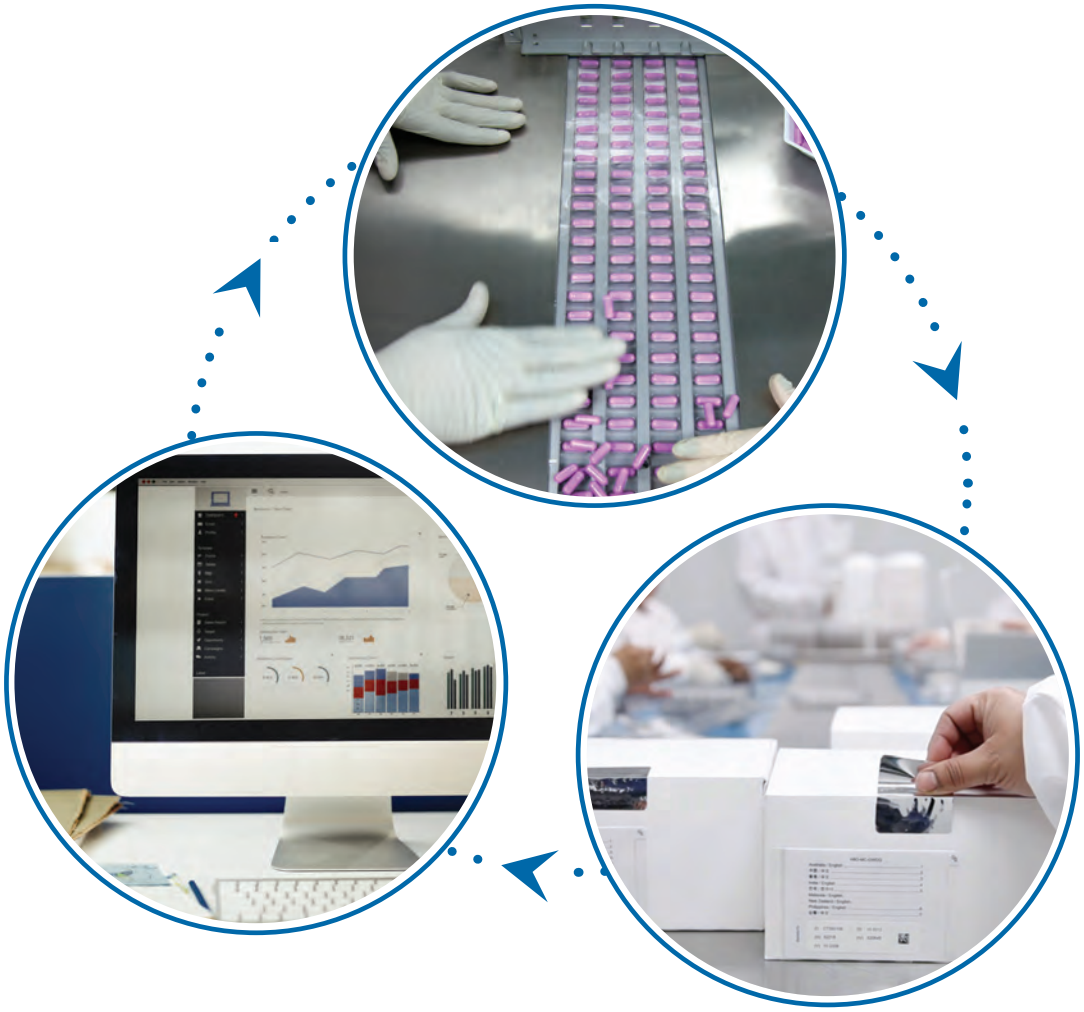

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