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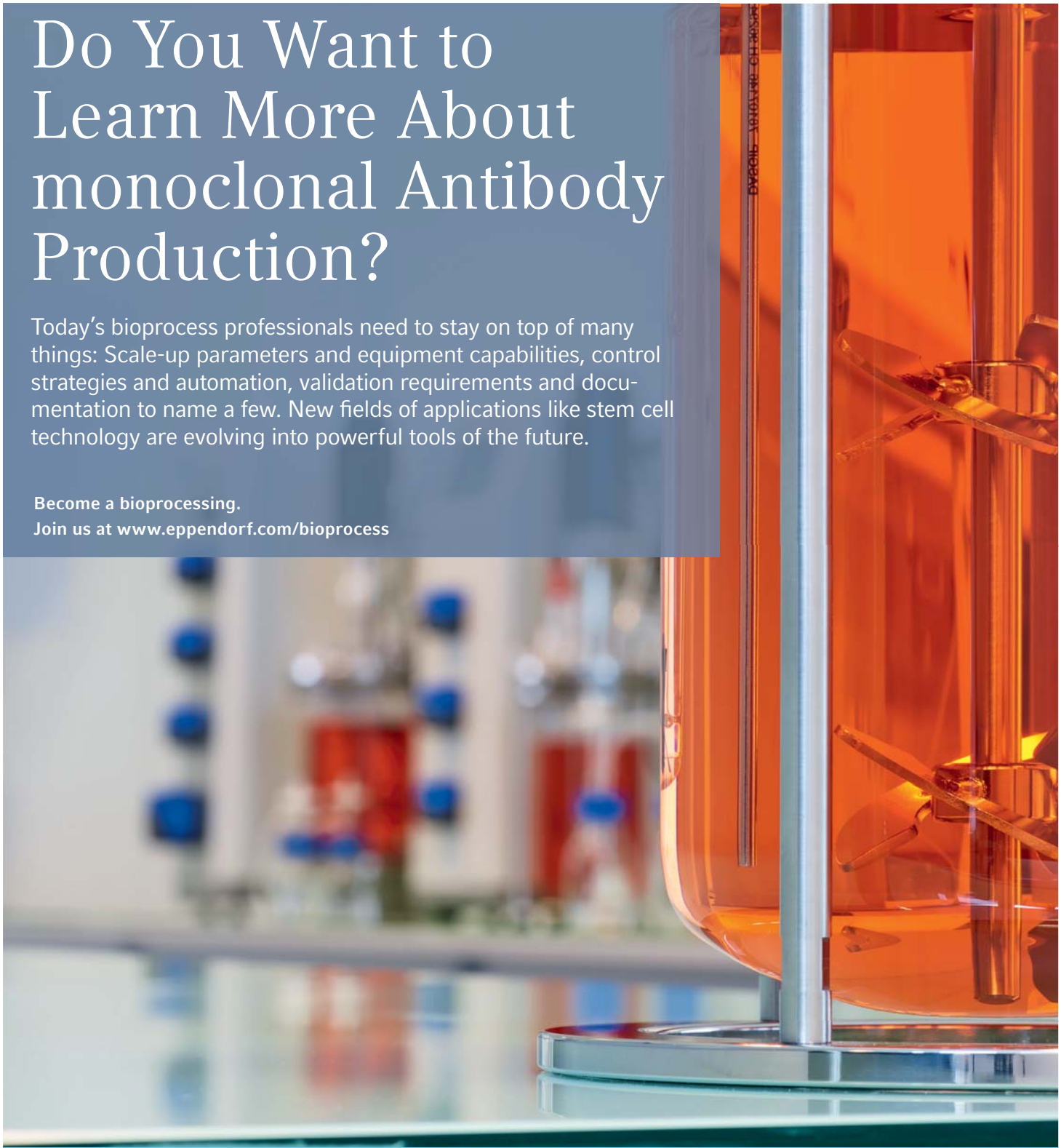

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Is it Time to Reevaluate Our Priorities?

The COVID-19 vaccines demonstrate what's possible when disease is tackled as a genuine priority

"The whole research and development community is working hard to bring us that [COVID-19] breakthrough sooner rather than later," wrote Stephanie Sutton in her November editorial (1). And here we are, just one month later, with not one but three breakthroughs.

Pfizer (2) and Moderna (3) are both claiming around 95 percent efficacy in their vaccine studies, involving 44,000 and 30,000 volunteers respectively. And then we had AstraZeneca and the University of Oxford announcing that their vaccine, which should be cheaper and easier to distribute than the aforementioned mRNA approaches, is 70 percent effective (4). In a serendipitous turn, some volunteers were mistakenly given shots half the planned strength, which turned out to be more effective than the original dose – 90 percent as compared to the original 60 percent (hence the 70 headline figure – and an additional dose of controversy).

It's important to not get carried away – however desperate we all are to see the back of this pandemic. As Peter Doshi writes in the BMJ (5), we don't know about the vaccines' ability to save lives, prevent infection, the efficacy in important subgroups, or the performance at three, six or 12 months. But if (and that's a big if) we now have the means to beat COVID-19 in the near future, the industry has managed to accomplish a feat that would ordinarily take years – even decades. How was this possible? And are there any lessons we could apply to other diseases?

SARS-CoV-2 may be, as Stat News pointed out (6), an easier target for potential vaccines than other pathogens. But a major factor has to be money. Both the funding received by companies developing vaccines (close to a billion dollars from the US government in Moderna's case), and the prospect of huge financial rewards should they succeed – a combination of state and market incentives.

As a global society, we must ask ourselves a big question: Are we really prioritizing medicine? We might not think of cancer or Alzheimer's as "emergencies" (unless we are directly affected) – but they have a combined economic impact that must surely exceed that of COVID-19 – especially over the course of decades. Though we couldn't go after one disease at the expense of all others (consider the hidden death toll of the pandemic), perhaps we could achieve remarkable things, if governments – with the support of the general population – made tackling diseases a genuine priority.

James Strachan
Deputy Editor

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Ending 2020 on a high: celebrating the annual Innovation Awards

the Medicine Maker

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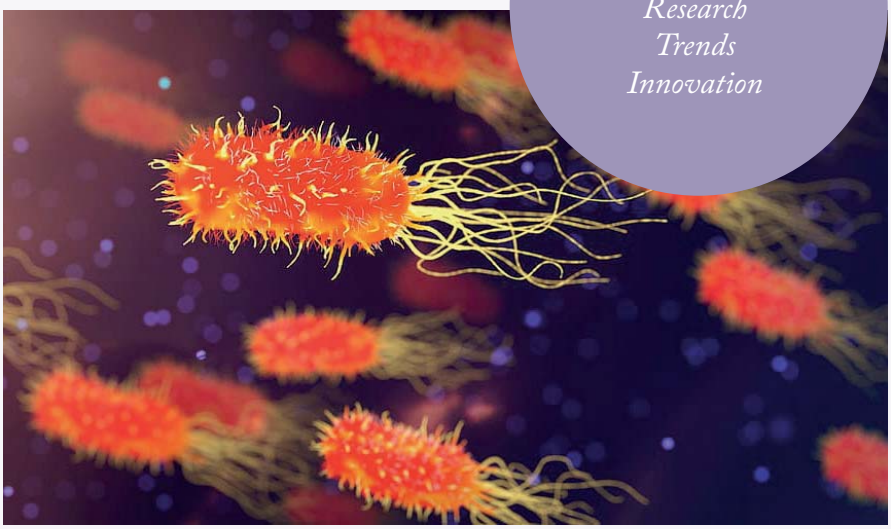
Upfront

Research
Trends
Innovation

Bacterial Boost

Can microbes enhance the efficacy of immunotherapy?



Why don't immunotherapies work for everyone? The answer isn't entirely clear – but new research published in Science sheds some light (1). According to Lukas Mager, a senior postdoctoral researcher at the University of Calgary and first author of the paper, specific bacteria in the gut microbiome play a significant role in the success of immunotherapies in treating certain cancers.

"Immune checkpoint blockade (ICB) treatment is used with great success in some tumors, but not all cancer patients respond due to primary – and later secondary – resistance to these therapies," Mager says. "Recent studies have shown that the efficacy of ICB therapy depends on specific bacteria, but it remains unclear how they elicit this enhanced response."

Mager and his colleagues decided to investigate the role gut microbes play in ICB treatment efficacy and found that certain bacteria produced a metabolite called inosine, which enhances the effect of immunotherapies in cancer. In mice, inosine – together with proinflammatory stimuli and checkpoint blockade immunotherapy – increased the antitumor capacities of T cells in multiple tumor types, including colorectal and bladder cancer, as well as melanoma.

Looking forward, the team hopes to translate their ICB-enhancing microbes to the clinic, but Mager sees challenges ahead. "We and others have identified several different bacteria and a metabolite that could be used as an ICB-adjuvant treatment in clinics. However, it remains to be seen which bacterium or mix of bacteria is most efficient and safe in humans." Further to this, the mode of application will likely require optimization to overcome colonization resistance in patients and to allow for the stable integration of ICB-enhancing bacteria in sufficient quantities over time.

The researchers are also investigating the microbiomes of tumors themselves. "Recent work has shown that tumors have their own distinct microbiomes (2). We have also observed differences between the fecal- and tumor-associated microbiome. Arguably, these tumor-infiltrating bacteria will have a strong impact on local tumor immunity," says Mager. He expects future trials to examine the likely intimate relationship between these bacteria and the immune system.

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INFOGRAPHIC

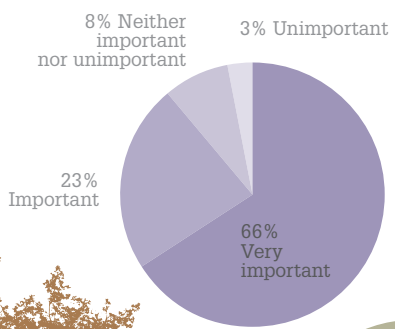
Green Progress

A report on biopharma cold chain reveals green goals for a more sustainable future

Key findings

- Sustainability is a talking point but green initiatives are not widely formalized
- Sustainability is already a factor in cold chain decision making
- Expectations are high for recyclable cold chain packaging materials and energy-efficient shippers

How important is sustainability to your business?



BUSINESS IN BRIEF

Criminal charges, drug pricing, and upgraded headquarters… What's new in business?

- Purdue Pharma pleaded guilty to three charges concerning its role in the supply of OxyContin, bringing an end to its civil case with the US Department of Justice. The charges included two counts of conspiracy to violate the Federal Anti-Kickback Statute – a law that prevents the exchange of items or services for reward referrals – and one count of dual-object conspiracy to defraud the US.
- Most Favoured Nation, a drug pricing policy, was set into motion in late November by President Donald Trump. The pricing model is expected to lower the cost of 50 prescription medicines in line with the prices paid by Europe's wealthiest nations. The policy will come into effect on January 1, 2021.
- In line with a new 15-year plan, Roche's Genentech is expected to almost double its headquarters space to 9 million square feet. The upgraded sites will support the company's R&D and manufacturing needs, and will accommodate an additional 12,000 members of staff.
- A collaboration between Gavi, The Vaccine Alliance, and the International Organization for Migration pledges to provide vaccinations for those affected by emergency or humanitarian crises, and encourage companies to consider those who may otherwise be missed in their COVID-19 responses. "Children from migrant, refugee, and displaced populations are too often overlooked when it comes to basic health care. This obviously becomes all the more important as we plan to roll out COVID-19 vaccines worldwide; we cannot allow these populations to miss out on what could be one of our best routes out of this pandemic," said Gavi's CEO, Seth Berkley, in a statement.

Full Power for 2021

Nominations for The Medicine Maker Power List will close on January 25

The Medicine Maker 2021 Power List will be published in April to celebrate the great minds and personalities that contribute to the development of new medicines – including small molecules, biopharmaceuticals, and advanced medicines. Nominations can be submitted using the quick form at http://tmm.txp.to/pl2021-noms.

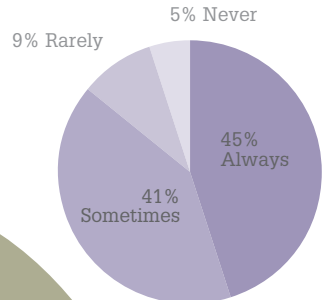
Who is eligible? You can nominate anyone involved in the development or manufacture of new medicinal products – and we invite nominations from all corners of the industry including big pharma, startups, research institutes, societies, regulators, NPOs, academia and more.

We want to celebrate the diverse talent and experience that makes the pharma industry tick – please join us!

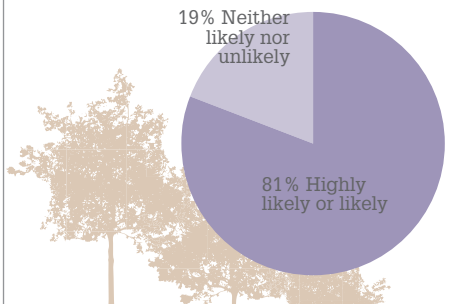
For inspiration or reference, the 2020 Power List can found at: www.themedicinemaker.com/power-list/2020

Questions? Email stephanie.sutton@texerepublishing.com

How frequently does sustainability factor into your cold chain purchasing decisions?



How likely are you in the future to use energy-efficient packaging?



Driving factors

- Preserve the planet
- Reduce waste
- Strengthen brand preference and outperform peers

Source:

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Pandemic Preparedness

What have we learned from the pandemics of the past? Experts give their view in a video discussion

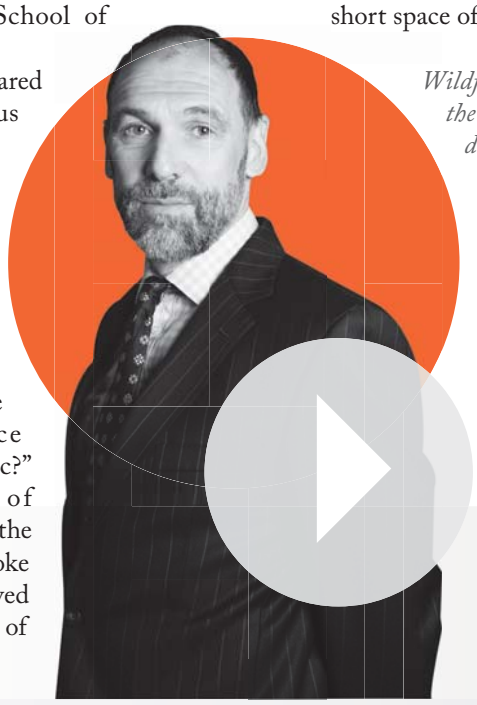
Why was the world so unprepared for a coronavirus pandemic? Long before 2020, scientific experts, the WHO, and even the World Bank pointed out that coronaviruses could be problematic. In some ways, we were perhaps lulled into a false sense of security by recent epidemics and pandemics. SARS and MERS did not spread extensively across the globe, and the 2009 H1N1 crisis was considered mild in comparison to 1918's Spanish flu.

"We took our eye off the ball – possibly in 2008 when funding for betacoronaviridae took a nosedive because we went into an economic crash," says Adrian Wildfire, Director, Scientific and Business Strategy at hVIVO, a clinical development services business.

Wildfire recently moderated a roundtable discussion for The Medicine Maker focusing on how previous pandemics have shaped responses to the COVID-19 crisis. The conversation involved Pieter Neels, Chair of the Human Vaccine Committee of the International Alliance for Biological Standardization; Marco Cavaleri, Head of Office, Biological Health Threats and vaccines strategy at EMA; Rebecca Cox, Professor of Medical Virology and Head of the Influenza Centre at the University of Bergen and Haukeland University Hospital, Norway; and Daniel Hoft, Professor of Internal Medicine at St Louis University School of Medicine, USA.

"We were not prepared because the previous SARS and MERS pandemics were far from our bedside," said Neels. "The 2009 H1N1 crisis was judged a mild influenza, so why should we have all these measures in place for such a pandemic?" As an example of complacency, before the COVID-19 crisis broke out, Belgium destroyed a strategic stockpile of millions of masks because it didn't think they would be needed. The masks were purchased over a decade ago because of fears of an influenza epidemic. However, Neels adds that we "simply could not imagine that the next pandemic would be on the same level as the Spanish flu."

But it's not all bad news. When it comes to vaccine manufacture, processes have certainly changed drastically over the last century – emphasized by the fact that the industry has been able to create new vaccines for COVID-19 in such a short space of time.



Wildfire, Neels, and the other participants discuss these topics and more in the video roundtable – available for free at http://tmm.txp.to/vaccineroundtable

Topping the Charts

Celebrating pharma's best employers

What makes a good pharmaceutical employer? Science asked over 7,000 people this question in its annual 'Top Employer' survey to determine the ingredients required for a positive work culture. For 2020, five key characteristics emerged as having significant importance to employees:

- innovative leadership in the industry
- respectful treatment of staff
- social responsibility
- loyalty
- a work culture that aligns with staff's personal values

Regeneron ranked top of the opinion poll – a victory that the company's executive vice-president, Drew Murphy, puts down to a science-first approach. "Our commercial people don't tell our researchers what to do. The scientists set the agenda. And if you do science the right way, you never really fail. You either succeed or learn something more valuable," he said in a statement (1).

The full list can be found here https://bit.ly/3nogIZ7.

Reference

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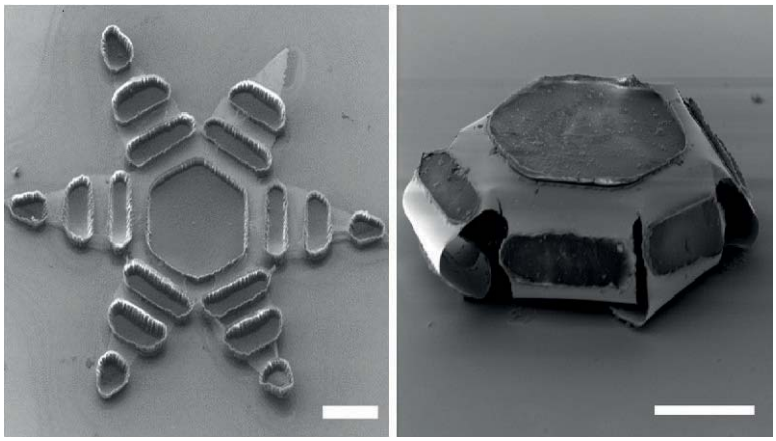
IMAGE OF THE MONTH



A Tight Grip

Researchers at Johns Hopkins Medicine have developed micro drug delivery devices called theragrippers that cling to the gut when exposed to the internal temperatures of the body – in a similar manner to parasitic worms!

Credit: Johns Hopkins University https://bit.ly/3nrqfi9

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QUOTE of the month

"The best possible position we could be in is where we have four or five or six of these vaccines available in the year 2021. The competition here isn't one of the other companies. It is the virus."

Alex Gorsky, Chairman and CEO at Johnson & Johnson at a virtual Detroit Economic Club conference.

The Advertising Push

How has pharma's ad spending changed in 2020?

The COVID-19 pandemic is adding additional momentum to the digital revolution in pharma. Now more than ever before, companies are becoming reliant on digital tools to facilitate their everyday activities – and the sector's approach to advertising is no exception. According to a report published by eMarketer, pharma's digital ad spending is projected to increase by 14.2 percent this year to an estimated US$9.53 billion. COVID-19 awareness campaigns and marketing for products related to safety and testing are cited as some of the key factors for this growth.

Although pharma is bolstering its mobile advertising capacity – with almost 58 percent of spending targeting the mobile platforms – it still falls short of the 68 percent average across other industries. It will be interesting to see how spending patterns continue to shift as the pandemic evolves.

Read the full report: https://bit.ly/3eVx48j.

In My View

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

3D Printing Unleashed

Additive manufacturing is so much more than just "cool" technology; it holds great promise for the biopharma industry

By Klas Marteleur, a Principal Mechanical Engineer at Cytiva, Uppsala, Sweden

Additive manufacturing – or 3D printing – is the process of creating a physical object layer by layer, using different materials, such as stainless steel, titanium or nylon. 3D-printed components find their way into diverse products, including jet engines, cars, and bioprocess instruments. Until recently, 3D printing was primarily used in product design departments to quickly create prototypes for testing purposes during development. Thanks to advances in printing technologies, manufactured (printed) components are equal to, if not better than, those produced by conventional technologies; in short, 3D printers are now ready to be used to improve end products.

In my view, the benefits of 3D printing technology are significant. Products will be smaller, lighter, and more optimized for the task; studies conducted here at Cytiva have shown that we can use 80 percent less material in some stainless-steel components using 3D printing! We can save even more material if we can consolidate several components into one (and we often can). By consolidating parts and reducing the number of joints in a bioprocess instrument, quality can also be improved and the risk of leakage reduced. It follows, then, that every instrument will be reduced in size and the productivity per square meter will improve. Imagine the innovation that could take place thanks to this increased design freedom.

Additive manufacturing will also help the biopharma industry reach its sustainability goals faster. Reducing material usage has a ripple effect. Lighter components require lighter frames or chassis to carry the components, and consolidation of components will lead to smaller instruments that require less space in the clean rooms. For example, chromatography instruments with many components and long lengths of piping could be reduced in size. A smaller and lighter instrument will also reduce the climate impact from transportation, and reduce the amount of chemicals needed to clean and maintain the instrument.

So what's the holdup? Why isn't the industry making greater use of 3D printing? To answer that, I need to go into more technical detail. Until now, the focus has been on the 3D printing machines themselves: making them better, faster, more accurate, and able to handle more materials. This work will continue but, for the components needed in life sciences products, post processing is equally important.

There are many different 3D printing technologies and, depending on the application, the resulting parts will require different types of post-processing. For example, if you print complex components, such as a manifold of a chromatography system, in stainless steel, you'll end up with rough surfaces directly from the printer. For use in a life science product, the component must have those surfaces polished –

"So what's the holdup? Why isn't the industry making greater use of 3D printing?"

"There are many different 3D printing technologies and, depending on the application, the resulting part will require different types of post-processing."

especially those areas in direct contact with the process contact – to improve cleanability and reduce the risk of cross contamination and bioburden. It is important to have control over each step in this manufacturing process to understand how they affect the result.

When it comes to the cleanliness of surfaces, the definition of "clean" depends on who you ask. If you ask a child if she washed her hands carefully before dinner and you watch her during the process, you might have a different opinion. And that does not necessarily mean that the child didn't try to clean her hands; more likely, it is that you have more experience and knowledge about what it takes to clean hands properly. It is similar in the 3D-printing industry.

There are many good print shops that can 3D print the physical part – and some that can even post-process it so it looks good, but there are not many that actually understand the requirements on a part that will end up in a life science product. It is important to have full control over the complete manufacturing process – from the raw material that goes into the 3D printer to the final post-processing and assembly steps – to ensure no harmful substances are able to leach into, destroy, or contaminate the customer process. To maintain full control, we decided to invest in essential technologies, including 3D printers and post-processing equipment.

The biggest threat to a wider implementation of additive manufacturing in the life sciences space is that we tend to stop challenging the way we do things today. If we just 3D print whatever designs we have today, little is won. For example, a simple sheet metal bracket can easily be made by bending a piece of sheet metal the traditional way, so 3D printing makes no sense. Instead, we need to rethink and redesign components and systems to unleash the power of 3D printing. We need to continue developing standards and technologies in parallel, while focusing on what is important and not discarding new solutions just because they might look different. Of course, we must never compromise on quality.

There are many opportunities with 3D printing, but there are no quick wins and plenty of challenges to overcome. Stamina, long-term vision, and the freedom to creatively challenge assumptions are all necessary to reach the goal. Naturally, an area with this much potential benefits from collaboration; working with customers and academia is crucial when it comes to understanding the real needs and opportunities.

By identifying pain points in existing products and then researching and developing new technologies to address those issues directly, I believe we can realize the next generation of biopharma equipment.

A Brave New World of Quality

Quality control must evolve to meet progress in biopharmaceutical manufacturing

By David Jones, Director of Technical Marketing and Industry Affairs at Rapid Micro Biosystems

Biologics are expected to reach 50 percent of market share of all therapeutics within 10 years (1) and, as a consequence, demand for biologics manufacturing is at risk of growing faster than capacity (2). Companies are now actively streamlining processes to run more activities in parallel, executing manufacturing development, scale-up, and validation of processes and clinical lots much earlier in the value chain, and increasing capacity to keep up with demand. They are also exploring new manufacturing approaches, such as continuous processing and modular manufacturing.

These activities will contribute to a brave new world of medicine making, but we also need modernized approaches to quality control (QC). To keep pace with accelerated and streamlined manufacturing, QC processes must be faster, highly automated, support confident decision-making, and ensure complete data integrity. The FDA has highlighted the importance of improved QC and stated that increased investment in manufacturing quality is a critical step towards minimizing disruptions in the supply of drugs (3).

A critical cornerstone of QC is environmental monitoring and in-process testing for microbial contamination. Current processes to detect microbial contamination are time- and labor-intensive; we need faster, better technology. Consider continuous manufacturing where drugs move through an integrated production workflow, without hold times between steps. The FDA calls the conversion to continuous approaches a "challenging but worthwhile transition (4)." While both batch and continuous manufacturing are subject to the same QC standards, however, monitoring is more frequent and must be automated in continuous manufacturing facilities to keep pace with production.

With continuous flow processes, the more rapid the turnaround of environmental monitoring and in-process testing, the better – these tests will identify a process that is going out of control and enable a quicker response. In addition, many of the raw materials used in the manufacture of biologics are expensive, and the ability to rapidly detect contamination will help reduce the risk of lost investment.

The use of modular cleanroom production facilities also benefits from rapid, automated QC processes. In contrast to conventional facilities that require significant capital outlay and long construction times, modular facilities are complete, turnkey units that are designed, validated and assembled off-site. Skid-mounted platforms in these facilities enable reconfiguration and upgrades without the costs and time requirements of major renovations. The environmental monitoring strategy can be identified before the installation of the facility, further accelerating deployment. This process includes the determination of high and low-risk contamination areas, the possible impact on the process, and identification of where to test and how. Automated QC systems for environmental monitoring and in-process testing can further increase the flexibility of modular manufacturing. These systems can be integrated into manufacturing, eliminating the need for a separate QC module. In this scenario, trained members of the manufacturing staff can feed samples into the automated QC system. The adoption of an automated approach for QC can also accelerate validation in terms of environmental monitoring, bioburden, and water systems. Integration of automated systems also eliminates the need for incubators and peripheral equipment, further reducing the time required for validation.

In addition to supporting new strategies, such as continuous processes and modular facilities, rapid and automated QC processes also enable wider adoption of digitization, where sensors and chemical testing methods are placed along the manufacturing line. As QC data come off the line, operators can respond more rapidly to process deviations. Automated QC processes provide an electronic output of data and can deliver a real-time display of conditions within the manufacturing facility, identifying possible hotspots of contamination with greater agility.

Conventional methods of manufacturing will continue to evolve – and drug manufacturers will embrace new technologies and workflows capable of delivering gains in speed, efficiency, and capacity, while preserving quality and data integrity. But if we, as an industry, are truly aiming for improved speed, patient safety, and reduced business risk in the years to come, then we cannot neglect innovation and implementation of modern QC approaches.

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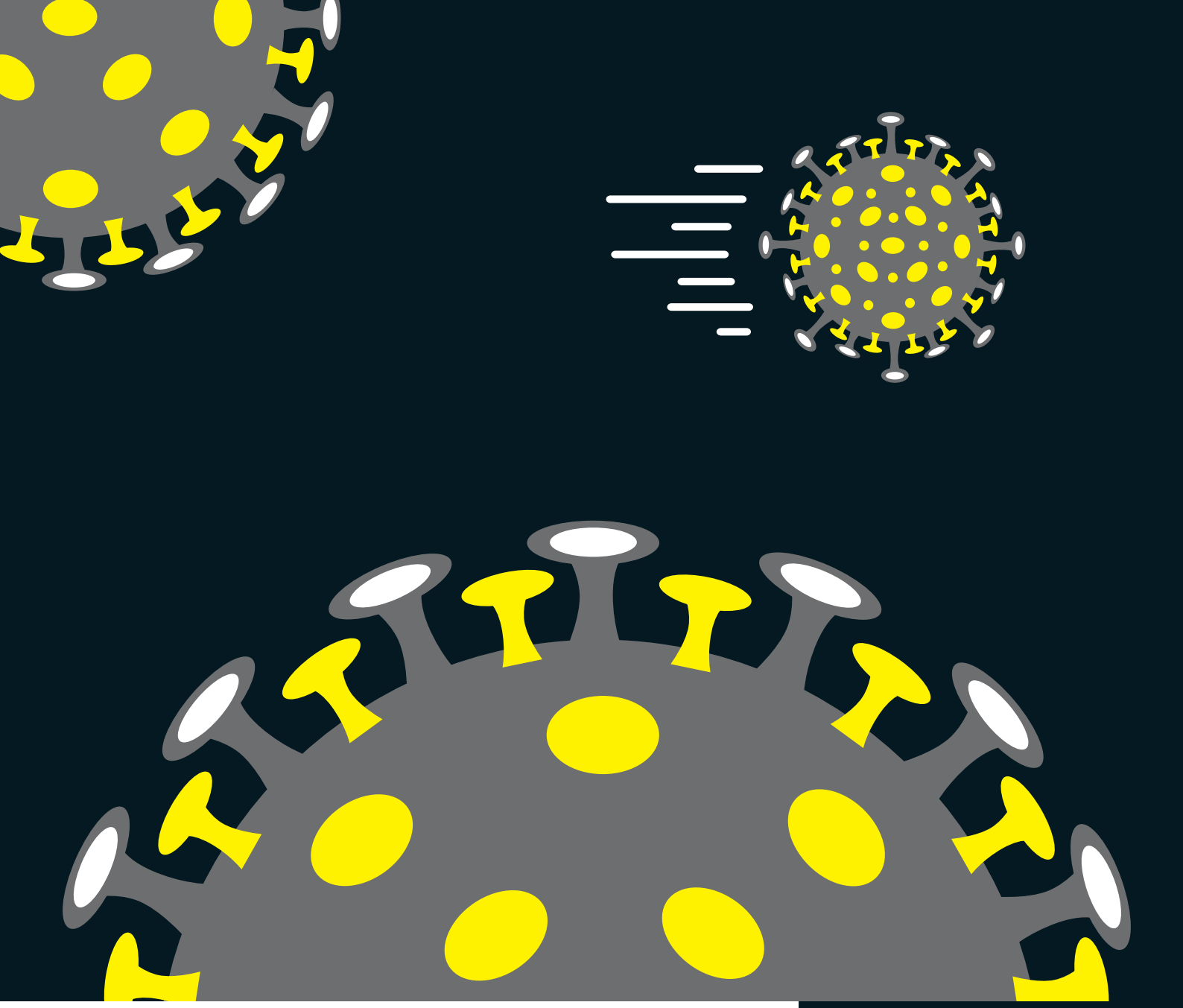

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INNOVATION AWARDS

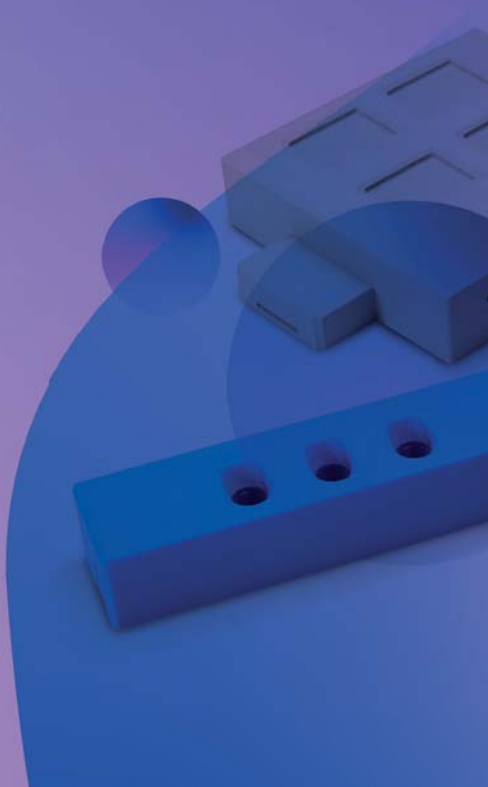
CELEBRATING THE MOST IMPRESSIVE DRUG DEVELOPMENT AND MANUFACTURING TECHNOLOGIES OF THE LAST 12 MONTHS

Welcome to the 2020 edition of a long-standing tradition at The Medicine Maker: The Innovation Awards! Here, we celebrate the top technologies released over the course of the year. (Nominations were collected via an online form available at www.themedicinemaker.com during 2020).

But which technology is truly the most innovative? Well, only you, our readers, can decide!

Go to http://tmm.txp.to/2020/innovationwinner to vote for your top pick. Please note: voting will close on March 3, 2020, and we'll publish the development story behind the grand winner in a 2021 edition of The Medicine Maker.

And, of course, the Innovation Awards will be back in 2021! Nominations will open in late Spring 2021. Sign up for our newsletter via the website to keep updated.

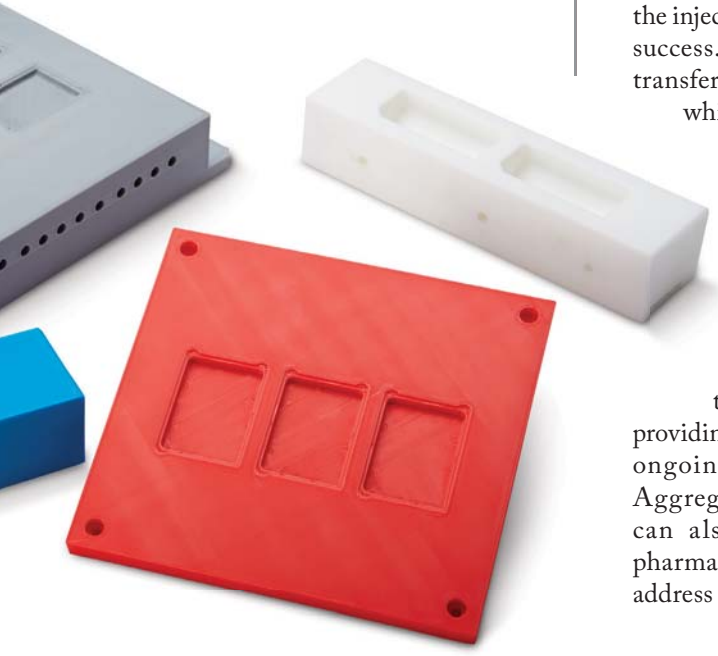


3D-PRINTED TOOL PROTOTYPING SERVICE

A prototyping service that creates test products using 3D printing technology

Maruho Hatsujyo Innovations

This 3D printing service can create sample blister cavities to help determine the most suitable options for particular medicines in terms of stability, childproofing, and material limits for filming/lidding. The results are almost identical to final production, potentially saving time and money compared with traditional metal tooling prototypes. After all, production tooling for blister machines is expensive – hence the need to get it right at the design stage. Historically, tooling lead times were measured in weeks; Maruho Hatsujyo Innovations claims that it can create 3D printed blister prototypes in days.



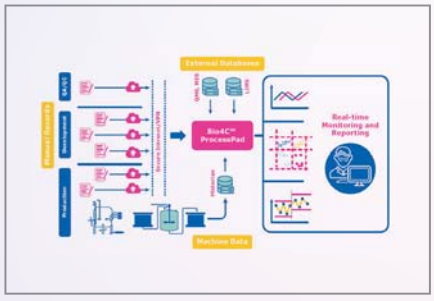
ADHEREIT 360 BASE AND ADHEREIT 360 CLIP

A connected solution for improving adherence in patients with auto-injectors

Noble and Aptar Pharma

AdhereIT can integrate with self-injection devices to support patients with initial onboarding and ongoing adherence to therapeutic treatments. The base and clip provide visual, audio, and haptic feedback during the injection process to guide dosing success. Encrypted data is then transferred to a smartphone app, which also incorporates patient resources, such as training videos, injection reminders, and drug reorder notifications.

Data can be shared with healthcare providers to track patient performance through a dashboard, providing real-world data to support ongoing therapeutic programs. Aggregated, anonymized data can also be made available to pharmaceutical companies to help address poor adherence.



BIO4C PROCESSPAD

Data collection, visualization, and analytics software for bioprocessing

Merck

Bio4C ProcessPad is a browser-based software platform for bioprocess monitoring, lifecycle management, reporting, investigations, and continued process verification. The software combines process data from different sources – including batch records, quality control results, standard databases, QMS, MES, LIMS, and data historians – into a single, integrated data source. It also features out-of-the-box data visualization and analysis tools to help scientists understand, explore, and analyze their data. The data can also easily be shared across geographies and organizational structures with operators, CMOs, and decision-makers.

According to Merck, without a structured process data management tool, bioprocessing scientists can spend over 80 percent of their time hunting and gathering data and only 20 percent on analysis. Bio4C ProcessPad was developed to help improve data analysis, facilitate quicker release of quarantined lots under investigation, and improve productivity and process monitoring.

BLAZAR PLATFORM

Multiplexed degenerate PCR-based platform for detecting viral contamination

Merck

The Blazar Platform expands the ability of conventional PCR. Degenerate primers are designed to target conserved protein motifs within viral families and multiplexing allows for coverage across hundreds of viruses. In addition, detection identifies the contaminating virus through sizing and sequence, facilitating faster investigation. GMP level viral screening can be achieved in one week.

The ability to screen biopharma products and their raw materials faster could be of significant interest to the industry. Faster viral screening can help biologic manufacturers reduce costs by accelerating the production process. According to Merck, the Blazar Rodent Virus Panel is already helping the industry by reducing the time required for cell line characterization from around three months to just four weeks, which should allow therapies to enter the clinic faster.

CERELLA

Artificial intelligence technology for active learning in drug discovery

Optibrium

Unlike many other AI platforms for drug discovery, Cerella is directly deployed by customers – enabled by a combination of on-premises software and cloud computing. The technology uses a peer-reviewed adaptive learning method, and directly connects with a corporate compound database to automatically update models when necessary.

Among other features, Cerella can "fill in" missing data to highlight high-quality compounds, to identify experimental outliers (to draw attention to experimental errors, unexpected structure-activity relationships, and false negatives) and to apply virtual screening across multiple endpoints to target the best compounds for synthesis.

GPEX BOOST TECHNOLOGY

Cell line expression technology for improving titers and cell-specific productivity

Catalent Biologics

GPEx Boost builds on the company's GPEx technology with enhanced benefits, including up to 10 g/l titer for standard mAbs (up from 7 g/l for GPEx), up to four-fold higher titers in difficult-to-express proteins, reduced ammonia build-up to improve cell growth and viability, and fewer process steps. The increased efficiency could lead to the use of smaller bioreactors (providing a greater number of facility fit options) or a reduction in the number of manufacturing batches necessary (potentially increasing production scheduling).

The cost of goods sold can be high for biologics, but improved titers can help reduce costs during development and commercial stages. Catalent Biologics claims that, based on expression data, GPEx Boost can significantly reduce the development batch costs for mAbs and recombinant proteins.

J.T.BAKER BAKERBOND PROCHIEVA

A recombinant protein A affinity chromatography resin for purifying antibodies

Avantor

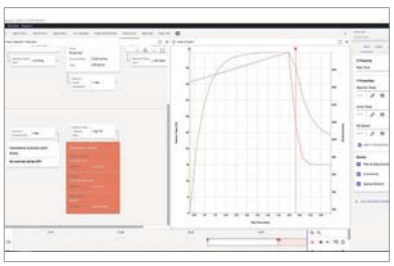
Protein A chromatography is a proven downstream purification step in manufacturing mAbs, but there remains a need to reduce total purification costs, while improving purity and yield. Bakerbond PROchievA is a high-performance protein A resin that uses a proprietary ligand to achieve dynamic binding capacity for mAbs and improved purification results in Fc-Fusion proteins and other emerging molecules. The resin is compatible with current manufacturing standards to ensure continuity in workflow processes and compliance protocols.

LABCONSOL

Software to automate and coordinate lab equipment

H.E.L Group

labCONSOL can act as a single point of control for around 140 separate control applications and over 900 device drivers. The engine can capture up to 100 data points per second. The developers say the software was based on feedback from scientists about wanting their teams to do the "right" experiments rather than the "easy" experiments. The software aims to make the right experiments as straightforward as possible, and includes drag and drop experimental setup capabilities and real-time data display capabilities that can be configured to user needs. Suitable for use in controlling potentially hazardous reactions, labCONSOL also includes multiple layers of warning and safety controls to protect both the user and the studied reactions.



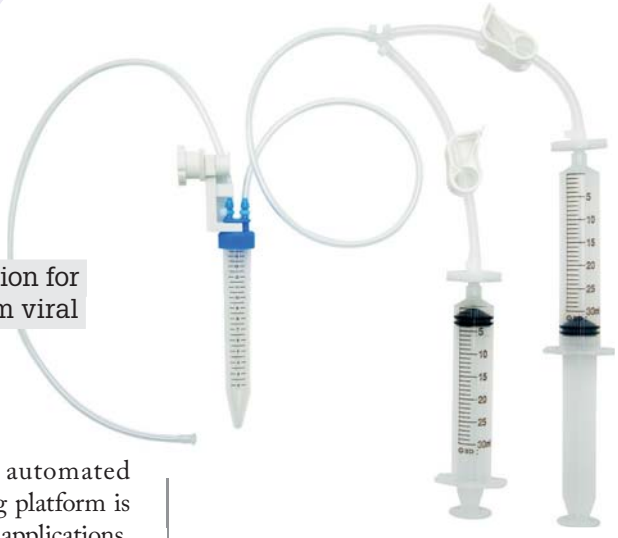
NEVOLINE UPSTREAM PLATFORM

An automated solution for intensified upstream viral manufacturing

Univercells Technologies

This integrated and automated upstream manufacturing platform is suitable for multiple viral applications, such as gene therapy and vaccine production. It enables intensified processing by chaining unit operations, such as culture, virus production, clarification, concentration, dilution, and conditioning to deliver concentrated, clarified bulk product. Single-use assemblies can be selected to accommodate different process configurations, enabling sequential, continuous, or parallel processing for time and footprint optimization.

The NevoLine Upstream platform has been designed for rapid deployment to overcome capacity and timeline constraints. At the core, the scale-X nitro structured fixed-bed bioreactor provides up to 600 m^2 of growth surface for high viral productivity, making parallel processing at commercial-scale possible in a 3 m^2 module. The high capacity, low footprint platform is controlled by a centralized automation system with pre-defined process recipes and in-line parameter control for batch-to-batch consistency.



OMNITOP SAMPLE TUBES ADJUSTABLE VOLUME SAMPLING SYSTEM (AVSS)

A single-use aseptic sampling product for bioprocessing

Avantor

Every drop is vital in cell and gene therapy production, but poor sampling methods can have a detrimental effect on the volume yield in any biopharma manufacturing process. Traditional open process sampling methods, which use an open bottle, conical tube, or other container, can risk contamination. The OmniTop Sample Tubes AVSS standardizes the sampling process and enables technicians to aseptically collect the exact amount of media required for routine sampling – and it is suitable for a variety of products, including mAbs, vaccines, gene therapies, and cell therapies. When used as part of scale-up and commercial manufacturing processes, it can potentially help minimize waste, reduce risk of contamination, and increase end product yield.

ORBITRAP EXPLORIS 240 MASS SPECTROMETER

High-resolution mass spectrometer for diverse small- and large- molecule applications

Thermo Fisher Scientific

Orbitrap Exploris 240 further expands on the Orbitrap Exploris platform to provide mass accuracy, sensitivity, and resolving power for both small- and large-molecule applications, irrespective of complexity or dynamic range, while minimizing time-to-results. The system uses the company's AcquireX intelligent data acquisition workflow to enable automation, while positive/negative mode switching enables comprehensive sample coverage and fast scan speeds. Regardless of application or sample complexity, the system is designed to provide high-resolution accurate-mass mass spec data that can be trusted. Instrument setup is facilitated by one-click calibration and ready-to-use method templates.

QX ONE DROPLET DIGITAL PCR SYSTEM

Multiplexed digital PCR system

Bio-Rad Laboratories

Bio-Rad's Droplet Digital PCR (ddPCR) technology can be used for the absolute quantification of target DNA and RNA via the generation and thermal cycling of thousands of nanoliter droplets. The QX ONE ddPCR system integrates the components of a standard ddPCR workflow, including droplet generation, thermal cycling, droplet reading, and analysis into one platform. The system features walk-away automation, reduced cost per sample, and the ability to optimize processes with a new multiplex supermix, and compatibility with existing supermixes. And, of course, it can be used with the company's QX ONE software.

SERIALIZED PRODUCT INTELLIGENCE (SPI)

Cloud-based analytics application that uses serialization data to offer supply chain visibility

TraceLink

Built on TraceLink's Opus Digital Network Platform, SPI allows companies to monitor, aggregate, and analyze serialization data, with a view to using that information to improve supply chains and on-time delivery of medicines. Users can examine the journey of each serial number to accelerate root cause analysis of internal and CMO operational issues, including reconciling all shipments and deliveries. It is also possible to compare operational events with regulatory reports to verify accuracy or to troubleshoot – and view compliance failures to drill down into root causes. Additional features include the ability to reconcile serial numbers and monitor commissioned lots.

SPI can be deployed quickly within existing TraceLink serialization systems. Finally, the ability to review messages and search audit trails are planned for a future release.

SMART CONTAINER

Containers laser-marked with data-matrix code to enable traceability and industry 4.0 standards in fill-and-finish

Schott Pharmaceutical Systems

A laser is used to melt a data-matrix-code onto the container the moment it is manufactured, allowing each vial to be traced throughout the fill-finish-process and beyond. The code withstands all following fill-and-finish steps and the marking process reduces particle contamination by avoiding additional substances for the application of the code.

Smart Container ensures each container is matched with the right content, cap, label, and secondary packaging based on the data stored in the system, and the containers can also help automate reject management and line clearance by collecting line performance data of the entire fill-and-finish process. In particular, the containers are well suited for lyophilization as the data matrix allows the exact position of each container to be tracked during freeze drying. The data can then be used to "map" the process to find specific defects.

SOTERIARX

On-dose authentication technology that allows solid dose medicines to be tracked from the manufacturer to the patient

Colorcon

SoteriaRx involves embedding micro tags into Colorcon's Opadry film coatings. The taggants are undetectable to the human eye, but can be quickly authenticated by in-field portable devices. Effectively, the pill, itself, becomes a barcode, meaning that authenticity can be confirmed by pharma companies – or patients – even without the product packaging.

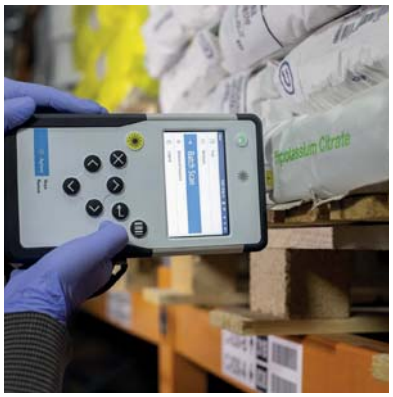
Counterfeit drugs are a major problem. Traceability and security measures focused only at the packaging level are not always enough to protect patients. Medicines made with on-dose taggants can be authenticated throughout the supply chain and are almost impossible for counterfeiters to replicate. The digitalization of medicines could be a major step forward in the fight against unauthorized and illegitimate pharmaceutical production, and an opportunity for regulators and industry to safeguard patients and improve supply chain efficiency.

VANQUISH CORE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC) SYSTEM

High-performance liquid chromatography systems for routine pharmaceutical laboratories

Thermo Fisher Scientific

Pharmaceutical QA/QC testing laboratories are expected to deliver precise and timely results. However, analytical scientists are often required to run methods on a diverse range of instrumentation, which presents challenges, especially when integrating new systems into existing infrastructure. Vanquish Core HPLC Systems are suitable for routine testing and quality control workflows, designed to deliver on-time results, simplify method transfer, and integrate with leading chromatography data system software platforms. Downtime is also reduced via a solvent monitor (which automatically tracks and determines mobile phase consumption and waste accumulation to prevent the systems from running dry or from waste overflowing) and continuous background monitoring of system health.



VAYA RAMAN

Spatially offset handheld spectrometer for raw materials ID verification

Agilent Technologies

Vaya is a handheld system that uses spatially offset Raman spectroscopy for raw material identity verification in pharmaceutical warehouses. The technology can be used by non-spectroscopists to verify incoming solid and liquid raw materials – through either transparent or non-transparent containers (including colored plastics, sacks, and amber glass), with a simple 'Pass/Fail' answer. There is no need for sampling and the rapid result means that testing is reduced from days to hours compared with conventional identification solutions for raw materials.

Methods for new materials are developed via an intuitive wizard, with the user guided through material and container spectroscopic evaluation, method development, and pharmacopeia-based identification method validation. Method assessment and spectral advisor features also allow users to develop robust methods by strengthening and challenging the method prior to deployment.

VIP LASER DRILL + NIR

Tablet laser drilling machine with near-infrared and vision inspection for controlled-release pharmaceutical products

Ackley Machine Corporation

The VIP Laser Drill + NIR incorporates near-infrared spectroscopy alongside precision CO2 laser drilling and vision inspection for the production of osmotic drugs. The machine uses NIR inspection to verify a tablet's enteric coating prior to laser drilling sub-millimeter sized apertures into modified-release products to achieve the desired dissolution rate and drug release profile. Vision inspection then confirms each aperture, while a patented fail-safe rejection system separates tablets with membrane defects from those with drill defects for further analysis.

The system has an output rate of up to 60,000 products per hour, a small footprint, multiple recipe management, and quick removal change parts.

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Speeding up the development of purification methods

Purification experts rely on the reproducible performances and secured availability of SkillPak pre-packed columns to develop purification methods for biomolecules

Since the beginning of the COVID-19 pandemic, the public has realized, more than ever, how essential the biotechnology industry is in securing our civilization's future. Downstream processing does not receive the same public attention, but none of the ongoing fights against the coronavirus would have been possible without proper purification of biomolecules. At Tosoh Bioscience, we always look at how we can enable our biopharma partners to provide safe and efficient therapies and vaccines against life-threatening diseases. Major tools to ensure fast scale-up of robust methods in the biopharma industry are pre-packed columns for early-stage development.

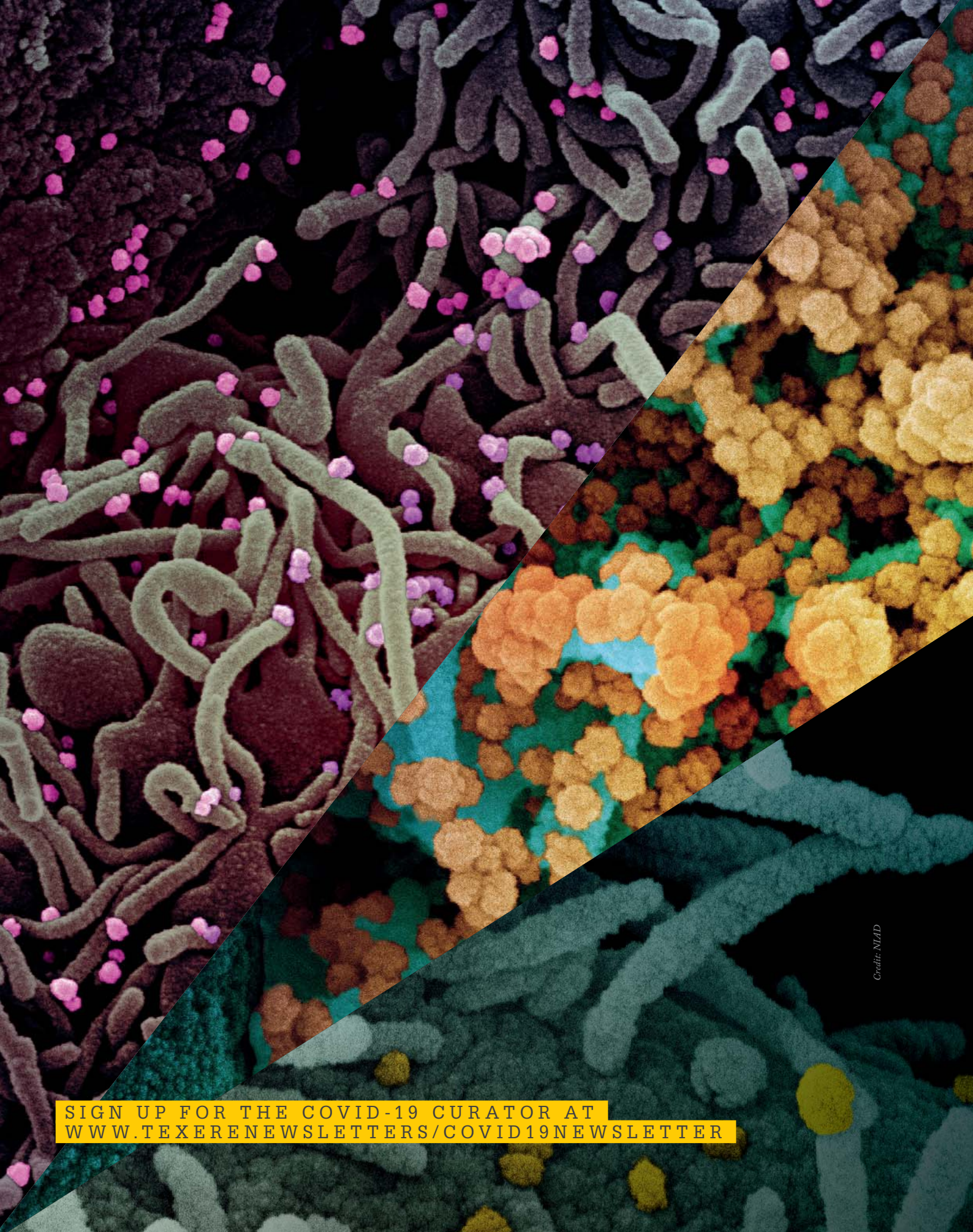
We launched the SkillPak® 1 and 5 mL pre-packed chromatography columns in April 2020. These columns have been welcomed by the biotech industry, as they offered a reproducible and efficient way of screening all innovative Toyopearl®, TSKgel®, and Ca^{++}Pure-HA™ process media. These columns guarantee optimal performance and can be operated with standard low- or medium-pressure liquid chromatography systems. They are reproducibly packed and take into account the varying compressibility of each resin – providing an accurate representation of conditions found in full-scale columns. In the past six months, we provided hundreds of columns to support the development of purification methods for monoclonal antibodies, antibody fragments, and oligonucleotides. Several of those projects have now entered clinical phases thanks to high throughput screening and easy scale-up.

We have developed our own solutions for the packing of small-scale columns, which not only offers the best performance for every single column, but also allows for better control of the whole supply chain. We aim to provide short delivery times for all columns, with well-planned production, strategic stocks on several continents, and integrated logistics. We have put our plan to test over the last several months, and have reached our targets day after day, despite employee lockdowns, supply route closures, and exploding demand.

If you want to see for yourself how SkillPak 1 and 5 mL pre-packed columns can help you develop better purification method faster, order a free set of columns today at: bit.ly/SkillPakTMM

TOSOH

bit.ly/SkillPakTMM



Credit: NIAID

SIGN UP FOR THE COVID-19 CURATOR AT
WWW.TEXERENEWSLETTERS/COVID19NEWSLETTER

Cutting Through the NOISE

LOOKING BACK ON 12 MONTHS OF COVID-19 RESEARCH

By Stephanie Sutton

There's no sugarcoating it: COVID-19 has been a disaster. Almost 1.5 million global deaths, as of early December, 64.5 million cases, and economies and livelihoods in tatters. Beyond the direct toll, the disease has affected many other aspects of health; for example, preventing patients from accessing elective surgeries or treatments for other diseases and conditions.

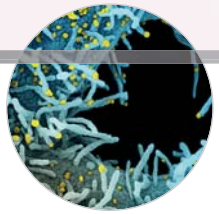
Scientists have scrambled (and are still scrambling) to understand more about coronaviruses and COVID-19 – and if there is one good thing to come out of the pandemic, it's how it has inspired so much research and collaboration. The pharmaceutical industry – viewed by some as a slow, lumbering behemoth – has demonstrated incredible speed, flexibility, and determination. Vaccine development typically takes years, but, at the time of going to print, we are at the start of the first wave of approvals after just ten (admittedly long) months.

The WHO has compiled a database of global literature on COVID-19, which includes more than 30,000 papers. Such a vast amount of scientific research – in such a short time – is incredible, but it can be hard to keep track of what is happening and to identify the most important research taking place. The task is complicated by media companies who pick and choose which science to report on. And when they do report on science, it may be skewed or overhyped. All of this adds to some serious online noise. How do you find out what really matters in the race to understand and fight COVID-19?

The COVID-19 Curator is run by my colleague, Michael Schubert, Editor of The Pathologist – a sister publication to The Medicine Maker. Every week, the Texere Publishing editorial team sift through and share the latest research on COVID-19, leaving Michael, Rich Whitworth (Content Director of Texere Publishing) and I to review and select the most novel or high impact efforts. The output? The COVID-19 Curator – you can sign up for free: www.texerenewsletters.com/covid19newsletter

For this feature, I've gone back through 11 months of news and our 36-issue strong archive to bring you a helicopter view of our fight against COVID-19. In a nutshell: though we still have a long way to go, there are many reasons to feel positive as we move into 2021!

PART I: CHARTING PROGRESS OVER TIME



JANUARY

Whole genome of 2019-nCoV sequenced
European Commission launches request for research proposals for COVID-19

FEBRUARY

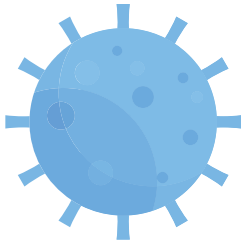
WHO officially chooses the name "COVID-19"
NIH begins clinical trial of remdesivir
European Commission issues statement on EU response: "According to the information provided by the national authorities, there is a strong overall level of preparedness with countries having response measures in place to provide treatment for the cases in the EU and to mitigate any further transmission within and into the EU." (https://bit.ly/3kElkIw)

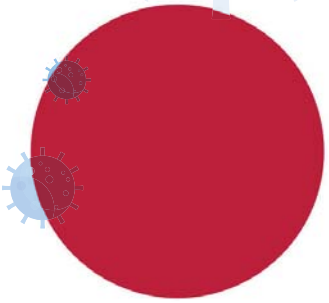
JUNE

Eli Lilly launches trial of LY-CoV555 antibody isolated from blood of COVID-19 patient
Systematic review and meta-analysis of all available evidence highlights benefits of physical distancing, masks, and eye protection in community and healthcare settings (https://bit.ly/38RA3hk)
FDA revokes authorization for chloroquine and hydroxychloroquine
UK government authorizes dexamethasone
Gilead's Phase III remdesivir trial shows that hospitalized patients in the five-day remdesivir group are 65% more likely to show clinical improvement by day 11 than those receiving standard care

JULY

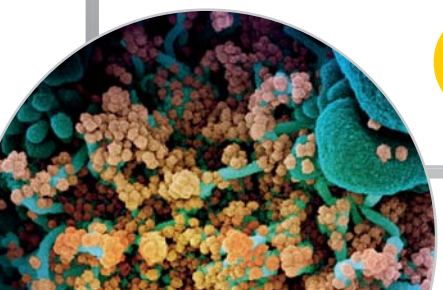
Commentary emphasizes benefits of voluntary human infection models for COVID-19 – with strict controls in place – and offers practical considerations (https://bit.ly/2IO4A4n)
Remdesivir receives conditional marketing approval from EMA
Japan approves dexamethasone
EMA says it will review study results on dexamethasone
Pfizer and BioNTech select lead mRNA vaccine candidate – after studying four options





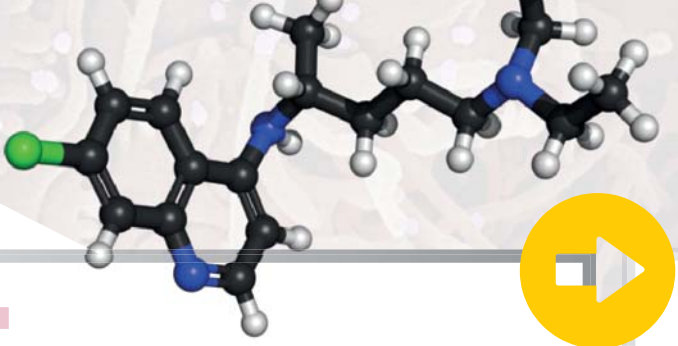
DECEMBER

UK MHRA grants temporary authorization to Pfizer/BioNTech vaccine



NOVEMBER

Regeneron told to modify trial of REGN-COV2
FDA issues EUA for Eli Lilly's bamlanivimab
Pfizer and BioNTech claim vaccine efficacy is 95%
Moderna says efficacy of mRNA-1273 is 94.5%
Interim data of Sputnik V suggests 92% efficacy; later increased to 95% efficacy
GSK and Medicago commence phase II/III study of CoVLP vaccine
Synairgen's inhaled formulation of Interferon-beta-1a, SNG001, passes small phase II study
AstraZeneca's Calquence (acalabrutinib) fails phase II trial
AstraZeneca and the University of Oxford announce interim results for vaccine; efficacy is up to 90%



MARCH

The WHO declared COVID-19 a pandemic
Gilead receives orphan drug designation for remdesivir in the US
Phase I study of Moderna's mRNA vaccine mRNA-1273 begins
Pfizer and BionTech announce co-development partnership for mRNA vaccines
FDA issues Emergency Use Authorization for hydroxychloroquine
FDA criticized for treating COVID-19 as a rare disease (https://bit.ly/2H8RluJ); Gilead withdraws orphan drug designation
By end of March, FDA had granted 20 EUAs for COVID-19 tests

APRIL

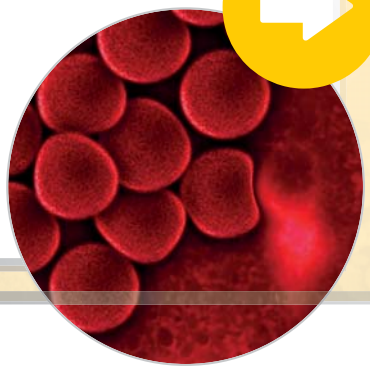
Early results from different studies suggest hydroxychloroquine, lopinavir/ritonoavir, and umifenovir are all ineffective at treating COVID-19 (https://bit.ly/2Helkla)
European Commission calls for partners to join Exscalate4Cov project, which will use supercomputers to screen databases of active molecules
Gilead highlights promising results from phase III remdesivir trial
AstraZeneca and the University of Oxford announce agreement for vaccine ChAdOx1 nCoV-19 (AZD 1222)

MAY

FDA issues Emergency Use Authorization for remdesivir
Japan approves remdesivir
Operation Warp Speed announced in US
FDA grants fast track designation to Moderna's mRNA-1273
WHO and Costa Rica launch Technology Access Pool
FDA research team review all clinical and research findings to date and compile key immunological events that existing drugs could target (https://bit.ly/2IM8bjZ)

AUGUST

FDA issues EUA for convalescent plasma for hospitalized COVID-19 patients
Russia approves Sputnik V vaccine
Gilead submits NDA to FDA for remdesivir
Gavi, CEPI and WHO launch COVAX initiative
Corona Accelerated R&D in Europe consortium launched



SEPTEMBER

EMA endorses use of dexamethasone
Regeneron's experimental drug REGN-COV2 added to UK's RECOVERY trial
Trial of Fujifilm's approved Avigan anti-influenza tablets meet primary endpoint

OCTOBER

Sanofi and GSK commence phase I/II trial of adjuvanted recombinant protein vaccine
Clinical trials for Eli Lilly's Ly-CoV555 treatment and J&J's JNJ-78436735 vaccine paused due to safety concerns
Remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon found to have little or no effect on overall mortality, need for ventilation, and hospital stay duration in WHO Solidarity Trial
FDA approves remdesivir
Results from phase I/II trial of Sinopharm's BBIBP-CorV vaccine suggest it is safe and well tolerated
PLACID trial in India shows convalescent plasma ineffective in preventing progression to severe COVID-19 or all-cause mortality (https://bit.ly/3kzuhTL)

PART II: FRONTRUNNING VACCINES

PFIZER AND BIONTECH

Candidate: BNT162b2
Type: mRNA vaccine

Notes:
- Requires two doses
- Vaccine must be stored at around -70 °C
- Companies expect to produce up to 50 million vaccine doses globally in 2020 and up to 1.3 billion doses in 2021
- Companies originally investigated four vaccine candidates before selecting BNT162b2

Vaccine has demonstrated efficacy of 95 percent in a phase III study. The study enrolled over 43,000 participants. 170 confirmed cases of COVID-19 were evaluated; 162 cases in the placebo group versus 8 in the vaccine group. The vaccine was approved for use in the UK in early December.

MODERNA

Candidate: mRNA-1273
Type: mRNA vaccine

Notes:
- Can be stored at 2-8 °C for 30 days
- Shipping and long-term storage require temperatures of -20 °C
- No dilution or special handling required at vaccination site
- Developed in collaboration with NIH and BARDA

Primary efficacy analysis of the phase III COVE study of the vaccine involved 30,000 participants and 196 cases of COVID-19 – of which 30 cases were severe. Vaccine efficacy against COVID-19 was 94.1 percent and 100 percent against severe COVID-19. FDA has told the company that a meeting is expected around December 17 to discuss the regulatory submission for an EUA.

ASTRAZENECA AND THE UNIVERSITY OF OXFORD, UK

Candidate: ChAdOx1 nCoV-19 (AZD1222)
Type: adenovirus vector vaccine

Notes:
- Expected to require storage around 2-8 °C
- EMA has commenced rolling review of the vaccine
- Trial was suspended in September but resumed quickly

This vaccine is expected to be cheaper and easier to distribute than the Pfizer or Moderna mRNA vaccines. However, questions have been asked about the vaccine's efficacy. A report from the trial seems to suggest overall efficacy of 70 percent, a lower efficacy of 62 percent, and a high of 90 percent. During the trial, some participants received 1.5 doses in error, which seems to correlate with the higher efficacy. Regulators were informed of the error and agreed that the trial could proceed.

ADDITIONAL KEY CONTENDERS:

Janssen: JNJ-78436725 (also known as Ad26.COV2.S) is a single dose adenovirus vector vaccine based on the same technology (AdVac) used in Janssen's Ebola vaccine, and investigational HIV, RSV, and Zika vaccine candidates. A phase III trial is underway.

Novavax: NVXCoV2373 nanoparticle vaccine has commenced phase III and been granted FDA Fast Track designation

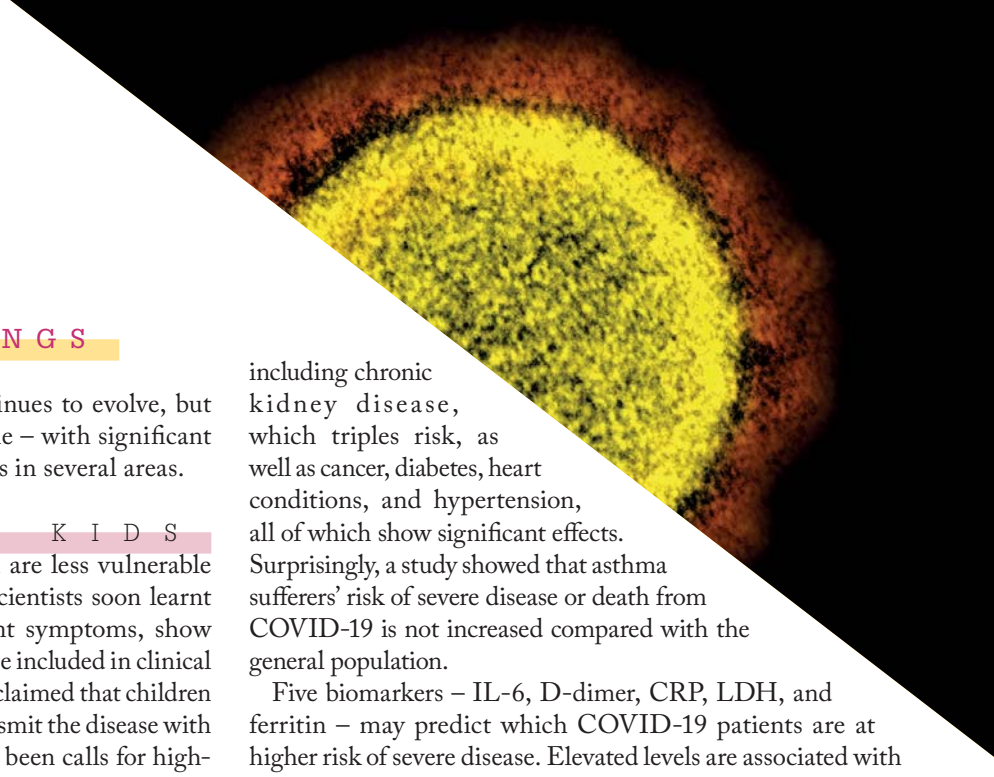
Sanofi and Translate Bio: mRNA vaccine induced high antibody levels in preclinical studies

Sanofi and GlaxoSmithKline: phase I/II trial of adjuvanted recombinant protein-based vaccine commenced in October

GSK and Medicago: phase II/III study commencing of CoVLP, which is composed of recombinant spike glycoprotein expressed as virus-like particles

Sinovac: inactivated vaccine undergoing phase I/II trials; recent death in trial not attributed to vaccine

Gamaleya Research Institute of Epidemiology and Microbiology: Sputnik 5 is already approved for distribution in Russia; Russia says vaccine has 92% efficacy



PART III: KEY RESEARCH FINDINGS

Our understanding of COVID-19 continues to evolve, but scientific ping-pong has been a key theme – with significant back and forth and contradictory findings in several areas.

COMPLICATED KIDS

Early on, it was suggested that children are less vulnerable to the effects of COVID-19. However, scientists soon learnt that children may present with different symptoms, show characteristic imaging findings, and must be included in clinical trials for the disease. Researchers have also claimed that children actually carry a high viral load and can transmit the disease with great efficiency – which is why there have been calls for high-quality testing and tracing for schools. Asymptomatic SARS-CoV-2 may be particularly prevalent in children. It is generally accepted that children tend to get COVID-19 less often than adults and have less severe symptoms. However, children infected with SARS-CoV-2 can experience catastrophic inflammation – and it may be possible for them to sustain significant heart damage. Discussions around exactly how susceptible children are to COVID-19 continue to take place.

LONGEVITY OF IMMUNITY

Studies seem divided on the longevity of antibody-based immunity to COVID-19, with some new studies revealing that robust neutralizing antibodies persist for months. For example, a survey of almost 6,000 patients finds SARS-CoV-2 antibodies persist for at least five months, suggesting possibility of lasting immunity after infection. Other studies, however, have shown significant drops in population antibody positivity.

But the outlook is bright for T cell immunity – with researchers showing long-lasting SARS-CoV-2-specific T cell immunity in recovered SARS and COVID-19 patients, and uninfected individuals. It is possible for a recovered COVID-19 patient to be reinfected, but this area is not yet well understood.

Would herd immunity ever be possible? Research into transmission dynamics suggests that a herd immunity strategy for COVID-19 management requires extremely sensitive and responsive fine-tuning, rendering it impractical for real-world situations.

RISK FACTORS

By linking routine health data to records of severely ill patients, researchers have sought to quantify clinical risk factors linked to death from COVID-19. A meta-analysis revealed pre-existing conditions that may increase risk of COVID-19 mortality, including chronic kidney disease, which triples risk, as well as cancer, diabetes, heart conditions, and hypertension, all of which show significant effects. Surprisingly, a study showed that asthma sufferers' risk of severe disease or death from COVID-19 is not increased compared with the general population.

Five biomarkers – IL-6, D-dimer, CRP, LDH, and ferritin – may predict which COVID-19 patients are at higher risk of severe disease. Elevated levels are associated with ICU admission, ventilation, and death. Tests have also been developed that offer insight into which patients are most likely to suffer severe disease or death from COVID-19. Airway cell immune analysis can identify patients at higher risk of severe disease, whereas red cell distribution width is highly correlated with mortality.

THE DRUGS DON'T WORK?

Hydroxychloroquine received early attention and emergency use authorization from the FDA – which was revoked in June. However, some scientists continued to believe that the potential of hydroxychloroquine was still worth exploring. In November, further studies emerged showing that hydroxychloroquine does not benefit adults hospitalized with COVID-19. In a statement, James P. Kiley, director, Division of Lung Diseases at the US National Heart, Lung, and Blood Institute, said, "We hope this clear result will help practitioners make informed treatment decisions and researchers continue their efforts pursuing other possible safe and effective treatments for patients suffering with this disease."

Although the case seems closed for hydroxychloroquine, what about remdesivir? Remdesivir also received significant attention early on – and approval in around 50 countries. Gilead has claimed that the trials have proceeded well, showing benefit in hospitalized COVID-19 patients compared with placebo and standard treatment, and reducing mortality by 70 percent in patients on low-flow oxygen. And yet the WHO's SOLIDARITY trial found that remdesivir, as well as several other treatment options, had little or no effect on overall mortality, need for ventilation, and hospital stay duration. Gilead has described the SOLIDARITY data as "inconsistent."

See references and further reading online at tmm.txp.to/1220/covid19

THE PANDEMIC DIARIES

Stephanie Sutton, Editor of The Medicine Maker and "a curator" on The COVID-19 Curator

At the start of 2020, I was naïve about what COVID-19 really meant. This isn't the first time I've written about a pandemic. Back in 2005/2006, there were fears about H5N1 and significant media attention, but the pandemic (thankfully) never materialized.

And then in 2009 came swine flu. I remember reporting on the deaths and cases in a weekly newsletter that I was responsible for at the time. The numbers were high, but the situation never felt out of control. A bottle of communal hand sanitizer appeared in the office – but most people didn't use it.

When COVID-19 began to appear in headlines, I wrongly assumed it was another flu we'd weather through. Even people directly involved in the pharma industry did not appreciate the severity of COVID-19 in January. One anonymous individual I spoke with explained that someone had mentioned COVID-19 at a briefing in January – not because they felt it was dangerous, but just as a "point of interest".

For me, the biggest shock was how quickly the situation escalated. At the start of March, I attended a fitting for my wedding dress – frankly without a care in the world. A few days later, Italy went into lockdown. Two weeks later, the UK followed suit.

Fortunately, scientific progress has been staggering – despite the aforementioned concerns, controversies, and questions. It is incredible to think that we already have results from three highly promising vaccine candidates – and even approval in the UK. But given that vaccine development typically takes many years, it's understandable that many people both inside and outside of the industry may experience vaccine hesitancy. Vaccine take up needs to be high to stall COVID-19 – so the industry has a responsibility to reassure everyone that speed has not compromised safety or quality standards.

Rich Whitworth, Content Director of Texere Publishing and "a curator" on The COVID-19 Curator

SARS-CoV-2 – or rather its devastating direct and indirect effects – certainly never crossed my worried mind in 2019 (despite subconsciously knowing that the risk was always there; if SARS and MERS weren't warning shots across the bow, I don't know what were).

Welcoming my daughter into the world in the year 2020 (hello, Mirajane!) has not been easy. Explaining to my three-year-old son (hello, Gray!) why he could not see "Grandma Buttons" or play with friends has not been easy. But, of course, I fully recognize the triviality of such personal struggles when viewed in full COVID-19 context. At the same time, I think it is important to remember that – COVID-19 or not – certain populations around the world are in a continual battle against deadly (though sometimes preventable or curable) diseases. Perspective can be a powerful tool.

Being part of the team behind The COVID-19 Curator has not only kept me abreast of the breakthroughs, the big questions, and the failures (all important) – it has also kept me sane. I've marveled at the speed of science and how it collides with clumsy politics. I would have been amused by the regular "ping pong" (as Steph like to call it) had it not been over such serious matters. And I've been utterly impressed by the seemingly unending sense of collective determination. When one well of hope ran dry, researchers in industry and academia had dug three more.

It's hard to talk about silver linings when faced with such a high and increasing death toll. But I welcome the growing understanding that we need adequate resources (funding) to tackle global problems. I also welcome the broadening acceptance that any solutions to this global problem must be accessible to all.

As 2020 draws to a close with positive news of vaccines with (almost unbelievably!) high efficacy – for many a light at the end of a very long, dark, and unsettling tunnel, I look forward to an even slightly more normal 2021.

Michael Schubert, Editor of The Pathologist and "The Curator" of The COVID-19 Curator

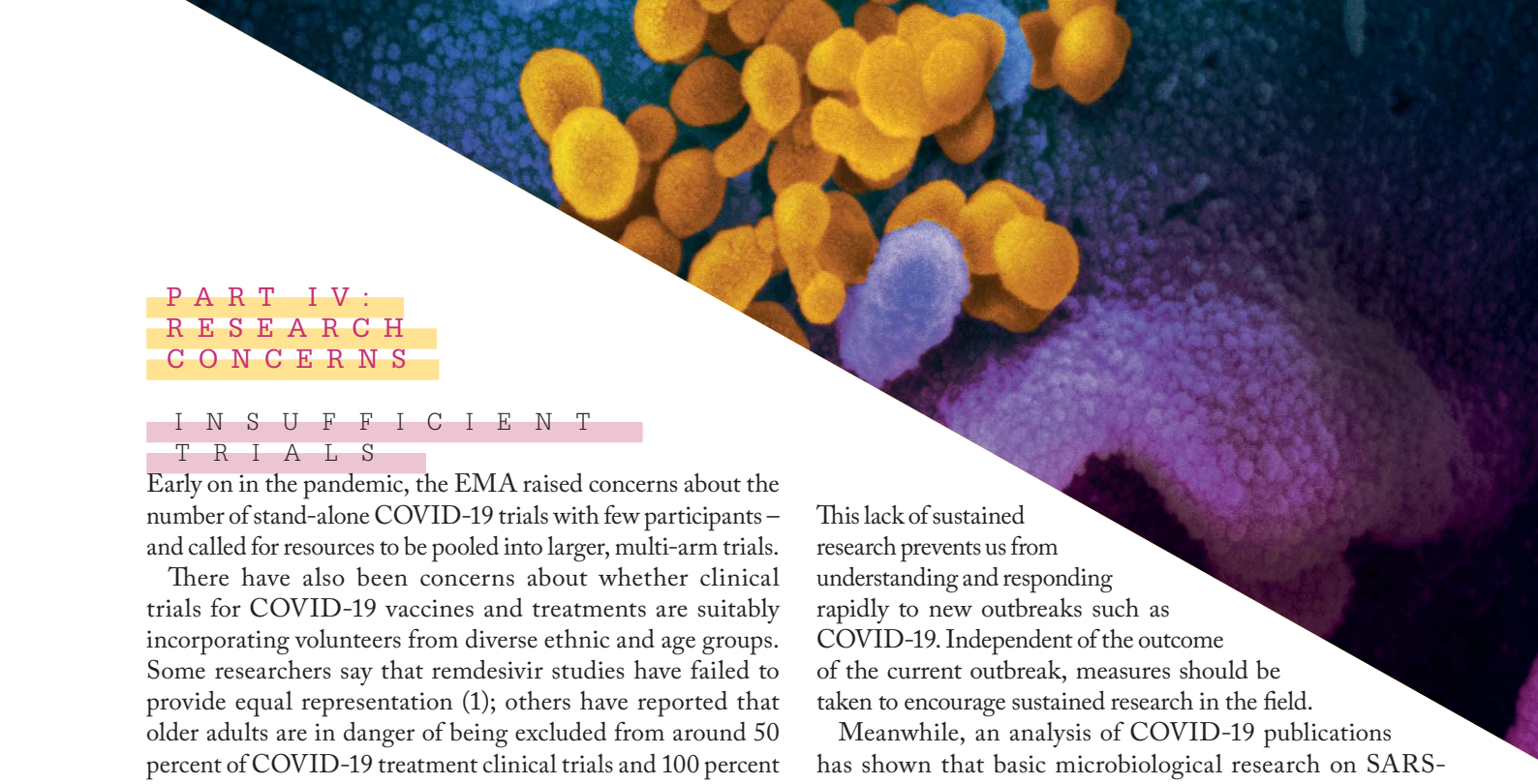
In the spring of 2020, I was engaged in online science outreach (somewhat presciently, as it turned out!). I hosted regular science chats with school-aged children, fielding questions on everything from "how can a spider bite give you superpowers?" to "how can we cure cancer?"

As March rolled on, though, the questions changed. "What is the pandemic?" "Do we have a cure for the coronavirus?" "Can people die from the coronavirus?" Tough questions to answer for any crowd – let alone schoolchildren.

And the answers to those questions changed, too. Initially, there was a lot of reassurance. The phrase "like a bad cold or a flu" made frequent appearances. Unfortunately, for nearly 1.5 million people, COVID-19 was far worse than any cold or flu they had ever encountered. And that's just the death toll; our ability to track and count those who suffer long-term consequences lags far behind.

This is the "new normal" – a world in which we stay indoors, wear masks when we venture beyond our thresholds, wash and sanitize our hands every time we touch something unfamiliar, and anxiously track reports on vaccine candidates.

Will a vaccine change the world? Undoubtedly. Will we return to our "old normal?" Only time will tell – but the tremendous efforts of scientific, medical, and pharmaceutical professionals globally have not gone unnoticed. As results and regulatory approvals roll in, we'll slowly see the world to come take shape – but it can only happen with appropriate oversight, open conversation, and a culture of shared scientific success.



PART IV: RESEARCH CONCERNS

INSUFFICIENT TRIALS

Early on in the pandemic, the EMA raised concerns about the number of stand-alone COVID-19 trials with few participants – and called for resources to be pooled into larger, multi-arm trials.

There have also been concerns about whether clinical trials for COVID-19 vaccines and treatments are suitably incorporating volunteers from diverse ethnic and age groups. Some researchers say that remdesivir studies have failed to provide equal representation (1); others have reported that older adults are in danger of being excluded from around 50 percent of COVID-19 treatment clinical trials and 100 percent of vaccine trials (2).

MOVING TOO FAST

Although the speed of action against COVID-19 is to be admired, questions have been posed: how could moving too fast prove harmful? For example, Douglas R. Green wrote an editorial in Science Advances, warning against speedy vaccine development at the expense of safety, highlighting evidence for potential ADE in SARS-CoV-2 (3).

Writing for the BMJ, Katrina Bramstedt raised concerns about substandard research (4): "No research team is exempt from the pressures and speed at which COVID-19 research is occurring. And this can increase the risk of honest error as well as misconduct. To date, 33 papers have been identified as unsuitable for public use and either retracted, withdrawn, or noted with concern."

In another BMJ article, Els Torreele explained how rapid vaccine development may lead to substandard first efforts that harm health, undermine public confidence in science, and squander financial resources that could otherwise be used to produce genuinely effective products (5). "By setting the performance bar far lower in COVID-19 vaccine development than what would otherwise be acceptable for a new vaccine, we are also unwittingly redefining the very concept of a vaccine – from a long-term effective preventive public health tool to what could amount to a population-wide suboptimal chronic treatment."

SUSTAINING RESEARCH

According to Dima Kagen, Jacob Moran-Gilad, and Michael Fire, research volumes tend to skyrocket after a coronavirus outbreak, but then drop precipitously after containment (6). This lack of sustained research prevents us from understanding and responding rapidly to new outbreaks such as COVID-19. Independent of the outcome of the current outbreak, measures should be taken to encourage sustained research in the field.

Meanwhile, an analysis of COVID-19 publications has shown that basic microbiological research on SARS-CoV-2 is lacking (7). Though perhaps understandable during a pandemic, this relative lack of lab-based studies is unique in research of other coronaviruses.

POLITICS AT PLAY

An opinion piece has also proposed FDA reforms to improve Emergency Use Authorization and drug approval processes in light of recent problems and controversies surrounding hydroxychloroquine, which had emergency approval revoked only a few months after issue (8).

More controversy surrounded the FDA's approval of remdesivir, with scientists raising concerns that the drug may be ineffective and questioning why the FDA did not consult external experts before issuing the approval. Some have suggested the approval may have been politically motivated (9).

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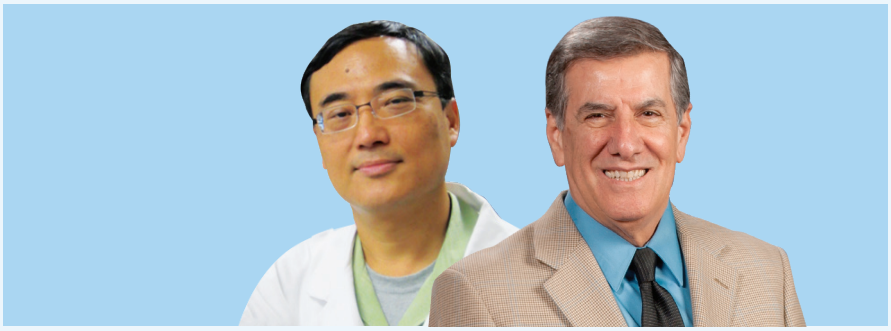
Up to the Challenge

As bioprocess technologies advance and drug markets evolve, new issues continually arise. How can manufacturers avoid the headaches?



Ma Sha and Kamal Rashid (www.cbetalbany.com)

Developing a new bioprocess is rarely straightforward – and optimizing an existing bioprocess is often no easier. And so it helps when manufacturers can work with instrumentation suppliers who are familiar with the problems they face; indeed, the shared understanding can benefit both parties. But what kind of challenges does the industry face, and how should they be addressed? Kamal Rashid (Founding Director, Center for Biopharmaceutical Education & Training CBET, Albany College of Pharmacy & Health Sciences, USA) and Ma Sha (Head of Bioprocess Applications, Eppendorf, USA) are well-positioned to answer these questions.

The fundamentals

Yield maximization, says Rashid, is an enduring challenge. "Yield is a function of cell viability and productivity – its maximization requires both excellent cloning technique and optimized media." Top tips include establishing where in the cell cycle the product is expressed (G1 or G2), as it may be possible to elongate the relevant phase – even a 1–2 hour extension can appreciably increase productivity. Rashid also emphasizes the importance of understanding the entire process, from cell-line design onwards. "Don't design your process on the basis of unverified assumptions – every cell line is different," says Rashid. Accordingly, Rashid advises monitoring and optimizing reactor conditions with regard to key metabolic pathways, and assessing the productivity consequences of any amino acid depletion. Similarly, manufacturers should optimize impeller RPM and heat transfer consistency throughout the reactor volume; remember that each cell line responds differently to mixing, aeration, and oxygen mass transfer. And to fully capture upstream yield improvements, consider investing in advanced downstream process instrumentation; after all, legacy systems are often inefficient. Finally, maintain strict controls throughout the process to avoid contamination-related batch failures. Meeting all these demands? Well, says Rashid, that also requires key personnel to be regularly re-trained.

The new hurdles

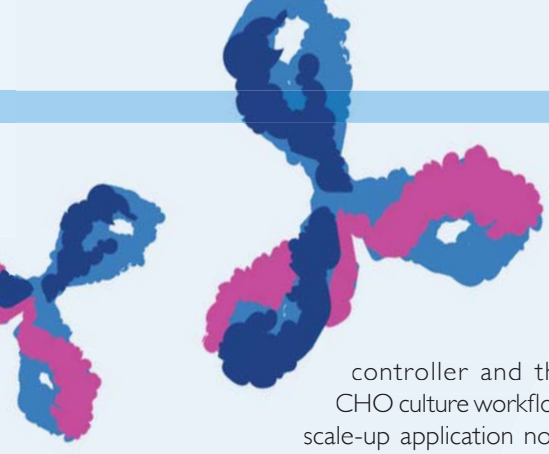
The plethora of new products entering development, including bi-specific antibodies, antibody fragments, and antibody drug conjugates, bring their own specific scale-up challenges; for example, bi-specific antibody manufacture is complicated by difficulties in the reproducible production of heavy and light chains, Rashid noted. More fundamentally, the entire sector is being affected by COVID-19; as Rashid says: "The industry must now develop the capability to rapidly produce stockpiles of vaccines and antiviral drugs." A feat that will require exploitation of advanced instrumentation. "Getting this wrong could cause costly batch failures and limit supply for patients," says Rashid.

He also says that cutting corners in equipment selection could result in significant negative impacts. To avoid expensive instrumentation mistakes, ask vendors for data demonstrating the suitability of their equipment for your process. "The best companies will have data from both in-house research and independent studies," says Rashid, before citing Eppendorf as an exemplar. "Their scientists are rigorous – they follow the data wherever it leads them." Being data-driven has enabled Eppendorf to continuously improve its technology portfolio, to the great benefit of the biomanufacturing industry. How do Eppendorf's scientists see things?

The Eppendorf way

Sha agrees with Rashid's analysis, and describes how "data-driven rigor" is part of Eppendorf's culture. "From its inception, Eppendorf Bioprocess Applications has reacted to the evolving needs of industry by developing advanced expertise and novel applications. When customers asked us to demonstrate antibody production in addition to cell expansion, we brought in a biosimilar CHO cell line, valued at $300,000, with high hmAb expression yield and standardized our CHO cell applications to include hmAb production."

Today, for every new product, Eppendorf provides a corresponding CHO cell bioreactor application note; examples include CHO fed-batch culture for the new SciVario twin



controller and the CHO culture workflow scale-up application note for the forthcoming BioFlo 720 Pilot Scale Single-Use Bioreactor (SUB) controller. Sha also emphasizes the two-way flow of information, recognizing that Eppendorf's success is partly due to its ability to learn from the customer. "Our collaboration with customers who were ahead of the curve in microcarrier and Fibra-cel® packed-bed Vero cell culture for vaccine production resulted in vaccine-related Vero cell application notes – and industry-wide dissemination of this new expertise (1,2)."

But Eppendorf's determination to solve customer problems goes much further than producing application notes. "Customers developing cell therapies needed products for stem cell cultivation," says Sha. "So Eppendorf developed stirred-tank bioreactor applications for large volume stem cell culture." Similarly, customers' pursuit of exosome therapy led to Eppendorf's development of a new stem cell application note for exosome production – and customer interest in alternatives to CHO cell-based antibody production resulted in Eppendorf developing the first bioreactor for in situ, Pichia-based production of full-length, human antibody Fc with humanized glycosylation. "When customers started exploring Pichia-based human antibody production as a potential future replacement of CHO platform, we were right there with them," says Sha.

It is perhaps unsurprising then that the industry frequently asks Sha's team for assistance with production problems. A common issue, Sha says, is CHO culture scale-up, where it is critical to maintain the cell growth profiles and antibody yields achieved at bench scale. "Strategies include keeping tip speed constant across bioreactors, matching oxygen volumetric mass transfer coefficients (K_La), and maintaining constant P/V scale-up – which is to say, maintaining constant impeller power per unit volume (P/V)." On that latter point, Eppendorf has now published multiple applications dealing with constant P/V scale-up and released many vessel power numbers (values required when developing scale-up processes).

And the industry will soon benefit from Eppendorf's new controller BioFlo 720; its "Scale-up Assist" feature uses a built-in constant P/V algorithm to automatically calculate agitation and gassing set-points needed for constant mAb yield in different vessel sizes. Remarkably, the BioFlo 720 will also provide Scale-up Assist for non-Eppendorf bioreactors. "It's just another benefit for our customers," says Sha. "Along with our application notes, our system makes it simple to maintain cell growth profiles and antibody production yields, all the way from 3 L bench scale to 250 L pilot scale."

Closing remarks

"Process optimization at bench, pilot, and production scale is critical for biomanufacturing success and requires advanced instrumentation," says Rashid. But adoption of novel technology can itself pose challenges for manufacturers; vendor support is therefore critical. Fortunately, Eppendorf Bioprocess is not just another bioreactor manufacturer; it offers customers not only the benefit of over one hundred application notes and industry publications, but also the problem-solving capabilities of two bioprocess application labs with PhD-level expertise. In short, customer service remains first and foremost in Eppendorf's culture. And Sha invites all interested parties to contact Eppendorf regarding to their specific needs: "Eppendorf Bioprocess strives to become the expert partner of choice in antibody production, vaccine, and stem cell culture markets and we are determined to meet customer needs at the highest level."

Monoclonal Antibody Production Methods (3)

- Batch:
  - All nutrients supplied in initial base medium
  - Lower productivity
- Fed-batch:
  - Nutrients are added to in-process medium, to avoid depletion
  - Higher productivity
- Perfusion:
  - Fresh medium is continuously circulated through growing culture, allowing simultaneous removal of waste, supply of nutrients, and harvesting of product.
  - Highest productivity

"Perfusion gives higher mAb yields than batch or fed-batch, but sacrifices the simplicity desired in a manufacturing environment." – *Ma Sha*

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Extracting Sense From E&L Science

Mark Jordi, President of Jordi Labs, discusses the latest in extractables and leachables science, including changes in the regulatory landscape and recent advances in methods for the identification and quantitation of leachables

Give us the quick lowdown on E&L…

Leachables are substances that come from – or "leach" out of – pharmaceutical packaging or manufacturing components and enter the drug product, resulting in patient exposure. Leachables can also stem from medical devices and transfer to the patient through contact with the medical device, either directly or indirectly. Extractables are substances that are observed to extract under laboratory conditions. Put another way, extractables are the components that may come out of a medical product, while leachables are compounds that do come out.

E&L analysis for drug products is required by regulators, including the FDA: "Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality or purity of the drug beyond the official or established requirements"(1). The goal of E&L analysis is to protect patient safety and support drug and device manufacturers by identifying toxic leachables before they reach the patient.

What guidance exists for E&L analyses?

2020 has been an exciting year in the world of E&L analysis because of significant changes in the landscape of available guidance. A partial list of the current US Pharmacopeia (USP) chapters that provide E&L guidance include:

- <87> Biological Reactivity Tests, in Vitro
- <88> Biological Reactivity Tests, in Vivo
- <381> Elastomeric Closure for Injections
- <232> Elemental Impurities - Limits
- <233> Elemental Impurities - Procedures
- <661> Plastic Packaging Systems and Their Materials of Construction
- <661.1> Plastic Materials of Construction
- <661.2> Plastic Packaging Systems for Pharmaceutical Use
- <1031> The Biocompatibility of Materials Used in Drug Containers, Medical Devices and Implants
- <1661> Evaluation of Plastic Packaging Systems for Pharmaceutical Use ad Their Materials of Construction
- <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
- <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems

Two additional USP chapters are also in development: <665> Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products, and <1665> Characterization of Plastic Materials, Components and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products.

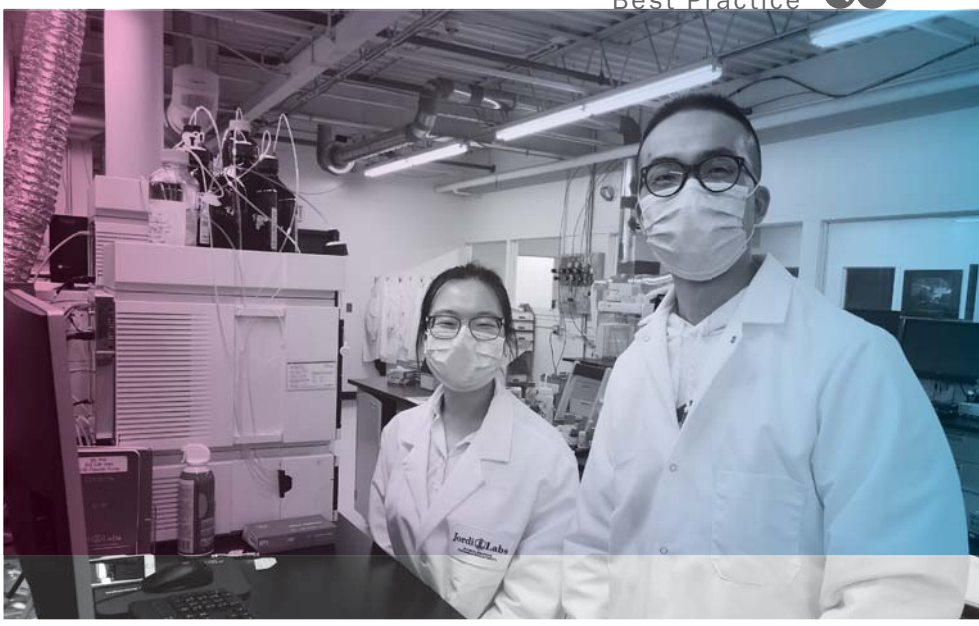
Chapters under revision include USP <661>, <661.1>, <661.2>, <1661> – December 1, 2025 is the scheduled implementation date for these revisions.

Though the USP chapters provide significant guidance, other sources of guidance also exist, such as the Product Quality Research Institute (PQRI) recommendations on orally inhaled and nasal drug products (OINDP): "Safety Threshold and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products." PQRI is also working on another document specific to parenteral and ophthalmic drug products.

Meanwhile, the BioPhorum Operation Group (BPOG) has published a revised document this year entitled "Extractables Testing of Polymeric Single-use Components used in Biopharmaceutical Manufacturing," which streamlines their testing recommendations. There is also ISO 18562, "Biocompatibility evaluation of breathing gas pathways in healthcare applications," and ICH has provided guidance applicable to E&L as a part of Q3C Residual Solvents and Q3D: Elemental Impurities. In July 2020, ICH also released a concept paper describing a new proposed guidance, Q3E, entitled "Guideline for Extractables and Leachables (E&L)" (2). This discussion has not included the EU guidance documents, but I think it's clear that the guidance for E&L of pharmaceutical products is rich and continues to expand.

In my opinion, the biggest news this year for E&L was the release of the much-anticipated ISO 10993-18:2020 medical device guidance, which became an FDA recognized consensus standard. This document provides a much greater degree of clarity surrounding best practices for E&L analysis of medical devices.

The document begins with a general description of the chemical characterization process. It then details the role and methods for obtaining information on the materials of construction, and for conducting compositional profiling as a starting point



for E&L analysis. The document then provides an overview of the E&L process, with guidance for assessing worst-case chemical release, establishing the analytical evaluation threshold (AET), and estimating chemical release using extractables studies and determining the actual release by subsequent leachables assessments.

The next significant section provides recommendations for the chemical characterization process, including selection of analytical techniques, the role of structural composition analysis, analytical methods and their qualification, and even reporting practices. It is then further supplemented with no less than seven annexes, providing an in-depth discussion on topics ranging from general principles of chemical characterization, extraction theory, qualification of analytical methods, and calculation of the analytical evaluation threshold (AET). This document also includes a great series of flow charts summarizing the chemical characterization process. It is by far the most comprehensive guidance for medical devices to date.

Can you tell us more about the importance of understanding "materials of construction?"

Actually, the first step in conducting a proper E&L analysis is the determination of the materials of construction and product configuration. This information is essential for several reasons. First, it establishes the theoretical worst-case chemical release; in other words, which configuration of the product will release the most leachables. Second, it informs all of the data interpretation that will occur in any subsequent E&L studies. Over many years of practicing E&L analysis – and seeing many thousands of extractable compounds – I've found that most extractables and leachables can be logically related to one of the materials of construction. For this reason, it is important that the chemists interpreting E&L data have a clear picture of the material composition and configuration.

A thorough understanding of the product should include information on each of the materials of construction, such as the identities of each polymer and its additives package. This should also include the proportion of each material and its physical state (surface area and topography), along with the geometric distribution of the materials in the finished article. Information on any expected processing residues is also helpful, and the potential effects of sterilization should also be considered. Finally, it is advisable to consider if any of the materials of construction are likely to have constituents from the cohort of concern (3). Given the importance of this information for informing an E&L study, it begs the question: how is this information determined? The supplier is generally the primary source for information about the materials of construction, but in cases where the supplier is either unable or unwilling to provide comprehensive information then compositional testing is the next best alternative.

Should leachables and extractables analysis be a targeted or untargeted screening exercise?

The process of extractables and leachables analysis can be broadly summarized in three steps: detection (determining which compounds are above the AET), identification, and quantification. Based on the above discussion regarding the importance of information about the materials of construction, it would be natural to conclude that E&L analysis is essentially a targeted exercise; that is to say, the process could be reduced to analyzing a targeted list of expected extractables to see which ones actually leach from the product. However, there is a problem with this idea. The history of recalls due to toxic leachables does not support the contention that all leachables are predictable. Consider for instance the Eprex recall due to unexpected dialkylphenol disulfide compounds from rubber stoppers (4). Though these compounds were related to a known constituent, the nature of these degradation products was not anticipated. Alternatively, consider the recall of breast implants due to tainted industrial grade silicones with unexpected impurities (5). These examples show that in many cases harmful leachables that lead to recalls (and hence, true safety concerns) are not adequately predictable based on the expected chemistry of the medical product under study.

The detection phase of an E&L analysis is intrinsically a screening process. Is this screening for known or unknown components? I would submit that the true answer is both. Proper practice of E&L screening includes both targeted and untargeted analyses. It should begin with a review of material chemistry and consideration of what extractables are

likely to be observed. If the material review indicates the potential for toxic leachables then a targeted approach is highly advisable. However, if no specific safety concerns are raised during material review, then E&L analysis reverts to what is essentially an untargeted analysis. There is little value in targeted approaches for compounds that are expected to be of low toxicological concern. Instead, the main goal at this stage is reliable detection of those compounds that are unexpected but of significant toxicity, or those which are of moderate toxicity but which are at such high levels as to be significant toxicologically.

Put simply, a properly protective extractables screening approach needs to be capable of detecting untargeted extractables and leachables. To accomplish this, our laboratories have designed a strategy called the multidetector approach, which is intended to provide a universal means for detection of unexpected E&Ls. The approach uses a combination of chromatographic methods and detectors, allowing detection of a very wide range of extractables. We use a triple detection liquid chromatography (LC) system, including a quadrupole time of flight mass spectrometer (QTOF-MS) coupled with an ultraviolet detector (UV), and a charged aerosol detector (CAD) – all combined in a single analytical instrument (QTOF-LCMS-UV-CAD) for detection of compounds based on three independent properties (ionizability, presence of chromophores, and non-volatility). This method is paired with the use of a dual detection gas chromatography (GC) system to aid in detection of volatile and semi-volatile species using electron ionization and flame ionization. Headspace GC-MS and inductively coupled plasma (ICP)-MS are applied for very volatile compounds (typically residual solvents) and elemental impurities respectively. This combination of methods provides comprehensive coverage for expected and unexpected impurities. A recent publication showed that the six analytical signals (five LC or GC detectors with LC-MS in positive and negative mode) allowed for up to 97 percent positive detection at the AET for a broadly constituted database of organic extractables (6). The approach increases the assurance that no toxic leachables will be missed during the early extractables screening work, increasing confidence that no unwanted discoveries will be made later in the product development lifecycle.

What should you do if you find unknowns that cannot be identified?

Based on USP <1663>, each identified extractable should be assigned a rating of "Tentative," "Confident," or "Confirmed." But one frequently asked question is:

"What do I do if I find a leachable or extractable using a detector that does not provide identification information, such as the UV, CAD or FID?" In general, if a signal is not observed in the initial LC-MS screening, it does not mean that identification by mass spectrometry is impossible. The use of high sensitivity QTOF instruments provide a greater opportunity to detect poorly ionizable species, while obtaining high mass accuracy and fragmentation data. This data is well suited to the task of identification. Our laboratories use both GC-QTOF-MS and LC-QTOF-MS (Agilent Technologies) instruments for this purpose. It is also often true that a compound not initially detected by MS can still be successfully analyzed using a more concentrated extract or an alternative means of ionization. For instance, if electrospray ionization was used in the initial analysis, a second analysis can be conducted with atmospheric chemical pressure ionization, or atmospheric pressure photo ionization, resulting in accurate mass information that ultimately leads to an identification.

A robust database of E&Ls also greatly aids in obtaining identifications due to the ability to use retention time matching. In our laboratories, we have combined more than 15 years of analytical data from a wide variety of medical products, building what I believe is one of the most comprehensive databases in the industry with more than 5,000 compounds. We use this internal database along with the Agilent's Masshunter Extractables and Leachables personal compound database and library to help identify unknown extractables. It allows us to combine two or more means of identification – retention time and mass spectral database matching – which increases the identification confidence level to "Confident" as per USP <1663>.

If these approaches do not prove adequate, then additional work using fraction collection is often the best alternative. The goal of this work is to isolate the unknown for further identification. The process typically starts by creating a more concentrated form of the unknown, which may be accomplished through an exaggerated extraction or sample concentration. Once the component is

purified, other chromatographic methods and detectors can be applied to aid in identification or, alternatively, traditionally non-chromatographic methods, such as NMR and FTIR, can be applied. In some instances, unknown peaks are actually compounds already observed by another chromatographic method, but for which a correlation has not yet been established. As an example, fraction collecting an unknown peak detected in LC-UV and subjecting it to GC-QTOF-MS could provide an identification that allows correlation between the two approaches. Alternatively, analysis by pyrolysis MS or any of a host of specialty techniques can be brought to bear to aid in identification once a compound is purified. In this way, an identity can be reached for essentially any compound.

Where do you see the future of E&L heading?

E&L work has the difficult objective of trying to detect, identify, and quantify any species that leaches or extracts from a medical product. The complexity of the array of different medical products, their materials of construction, and the development of novel materials means that the universe of potential E&L is large and ever expanding. Developing methods suitable for the detection of this universe of extractables remains a daunting analytical goal and, in our labs, has been answered by the development of multidetector systems. We believe that the application of more detection methods will become more standard as a greater understanding of the limitations of only LC-MS/GC-MS detection approaches becomes apparent. No single chromatographic detector can detect all analytes.

Obtaining "Confident" or "Confirmed" identifications also requires significant analytical expertise, including the development of large databases. I believe the future of E&L identification will be dependent on the development of very large and comprehensive commercial databases that allow for confident identifications. Obtaining accurate surrogate standard quantitations will also remain a hot topic, especially for exaggerated extractions of complex medical products where a large number of species need to be simultaneously quantified and formal quantitation is impractical.

I expect rapid change specifically in the requirements for E&L for medical devices, but also for combination products. This trend will be primarily driven by the release of the ISO 10993-18 guidance, which includes changes to the extraction process, such as an emphasis on exhaustive extractions for all permanent contact devices and a firm emphasis on using three solvent extraction studies (polar, mid-polar, non-polar). Though this may have been best practice in the past, today it is essential for most submissions. In the last two years, a much greater emphasis on quality controls has emerged. Triplicate analyses are now widely used to gauge overall analytical precision. A consistent requirement for spiking studies as a means to prove the recovery of chemically relevant compounds during sample preparation is now widely cited. There is also greater scrutiny regarding aspects such as surrogate standard selection, number of surrogate standards, and confirmation of quantitative accuracy through mass balance between NVR results and results from chromatographic methods. Even highly technical details, such as selection of an appropriate uncertainty factor in the AET calculation, are frequently discussed and questioned. Overall, there has been a significant increase in regulatory scrutiny of chemical characterization data and a greater emphasis on quality control. Moving into the future, we see this trend of increasing quality requirements continuing – especially for medical devices.

At the same time, we also see a growing complexity in drug formulations, which is driving the need for more advanced instrumentation and more skilled method development. Biologics and drug products containing significant amounts of non-aqueous components increase the extracting power of the drug product and the complexity of analyzing the drug matrix. Development of robust methods for quantitation of multiple leachables within a complex drug matrix requires significant expertise. The addition of biological components, such as proteins, or polymeric surfactants also adds additional challenges in sample preparation. It is essential that the laboratory has the experience and the necessary analytical tools to deal with the increasing complexity.

E&L analysis remains an essential part of ensuring medical product safety. It answers the big picture question, "What comes out of the drug packaging or medical device that could adversely affect the patient?" The complexity of medical products and the difficulty of the objective means that the industry standard practice to E&L is likely to continue to evolve as discoveries and innovations are made in analytical chemistry. I feel certain that E&L will remain an interesting, exciting, and challenging field of study for many years to come!

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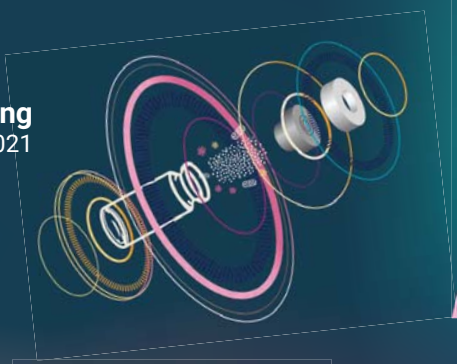

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Putting Sleeping Sickness to Bed

How can we eradicate this fatal tropical disease once and for all?

In 1990, serious inequalities in global R&D were highlighted in a report penned by The Commission on Health Research for Development. According to the independent healthcare body, the world's poorest nations accounted for up to 90 percent of the global disease burden – but only 10 percent of research was geared toward treating the conditions that caused such significant morbidity and mortality (1). Three decades have passed since these findings were first published, and the international community has made strong efforts to address the disparity that exists between healthcare systems and to find solutions to the treatment of neglected diseases.

Today, many companies have aligned themselves with the WHO's Neglected Tropical Disease (NTD) Roadmap 2030 to "respond to NTDs over the next decade (2)." And, to that end, Sanofi has been working with the Drugs for Neglected Diseases initiative (DNDi) on a new treatment for sleeping sickness – also known as human African trypanosomiasis (HAT). Transmitted by the tsetse fly, the condition is characterized by the entry of a parasite, Trypanosoma brucei, into the host's bloodstream, lymphatic system, and eventually central nervous system. The first stage of the disease causes lymph node enlargement, fever, and headache; the second results in serious neurological changes, including sensory disturbances, poor coordination, and errati sleeping patterns.

"Without prompt diagnosis and treatment, sleeping sickness is usually fatal," says Philippe Neau, Head of Neglected Tropical Diseases at Sanofi Global Health. "The disease is also considered endemic in 36 sub-Saharan African countries, where around 60 million people are estimated to be at some level of risk of HAT – primarily those living in poor, rural, and remote parts of East, West, and Central Africa, where health infrastructure is poor or nonexistent."

Sanofi and DNDi are co-developing a drug – acoziborole – to treat HAT that, once approved, will be distributed at no cost to patients or governments (3). "Acoziborole was identified by researchers from the University of San Francisco along with our biotech partners at Anacor and Scynexis," says Antoine Tarral, Head of the HAT Clinical Program at the DNDi. "We selected the compound for our lead optimization program and received new chemical entity status in 2009." The compound is the first new chemical entity from DNDi 's lead optimization programme to enter clinical development.

Though several medicines already existed, the discovery of acoziborole marked the start of a new approach to HAT treatment. "Until 2009, treatments for sleeping sickness were toxic and complex. They included an arsenic derivative called melarsoprol that brought about such severe pain when administered that it was known by patients as 'fire in the veins.' Devastatingly, it killed one in 20 people," says Neau. And though these toxic treatments were replaced by the safer combination therapy nifurtimox-eflornithine (NECT), it too was imperfect – hampered by logistical concerns in remote regions and the need for trained nursing staff for administration and hospitalization for patients.

A new era in HAT R&D

Before collaborating on acoziborole, DNDi and Sanofi worked together on fexinidazole – the first all-oral treatment for HAT, which made it easier for patients to avoid the challenges of systematic hospitalization and lumbar puncture associated with NECT. Clinical studies began in 2009. In 2018, the 10-day treatment received a positive scientific opinion from the European Medicines Agency and was granted market authorization to treat patients in the Democratic Republic of Congo (DRC). Though the partners believe the rollout of the drug was "successful," the 10-day commitment to treatment could be difficult for patients in the most remote areas – a single dose would be ideal for them. Acoziborole, on the other hand, is a single-dose treatment and the partners hope that it can be used alongside a rapid diagnostic test, which would simplify the process even further.

Unfortunately, says Tarral, "HAT is complicated to diagnose because many symptoms displayed by patients are nonspecific and accurate tests require skilled personnel." In many disease-endemic areas, staff simply aren't available in the numbers needed to effectively diagnose the patient population, resulting in many detrimental diagnostic delays. Despite these challenges, he remains optimistic. "Current tests rely on the detection of parasites in patient cerebrospinal fluid as well as white blood cell counts. We don't have the molecular biomarkers necessary for an improved, easy-to-use test, but we are optimistic that the industry will create reliable options in the future."

Acoziborole is currently undergoing phase II/III trials in the DRC and Guinea and is being tested against some of the most common strains of the disease. "Recruiting patients was challenging," says Tarral. "Given the aforementioned diagnostic challenges, finding people with confirmed cases and robust documentation to allow their participation in trials wasn't easy. We also had to ensure that they could be screened and tested close to their homes."

Beyond recruitment, the DNDi also needed to build some of the infrastructure necessary for the trials to take place. "To allow investigators to work in the best possible conditions, we were involved in the reconstruction of labs, hospitals, and

Credit: Neil Brandvold-DNDi

Therapeutic Altruism

With Phillipe Neau

Devastating HAT epidemics have occurred throughout the 20th century but, following the neglect of control efforts implemented until the 1960s, the 1990s saw a dramatic resurgence of the disease. The WHO reported almost 40,000 new cases in 1998 but estimated that approximately 300 000 cases were undiagnosed and untreated (1). In response, the WHO passed a resolution in 1997 to raise awareness of the disease, promote access to diagnosis and treatment, and strengthen control and surveillance.

In July 2000, the WHO intensified efforts to achieve these goals by forming global alliances with United Nations agencies (under the Program Against African Trypanosomiasis, PAAT), national governments (under NSSCPs), and the Organization of African Unity. The result was the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC). Another key alliance was the formation in 2001 of a long-standing public-private partnership with Sanofi, which would make it possible to distribute vital drugs to treat HAT and other NTDs in endemic areas free of charge. The partnership also provided funds to support screening and surveillance reports, improve treatment centers, train local health workers, and create research and development programs for new treatments.

At Sanofi, we cemented our commitment to the goal of eliminating HAT by signing the London Declaration on Neglected Tropical Diseases in 2012. The declaration focused on the commitment of a range of actors from the public and private sectors to control or eliminate 10 infectious diseases (including HAT) that affect the world's poorest populations. In this context, we contributed to the elimination of HAT as a public health issue by aligning our objectives with the WHO's goals and freely supplying drugs to ensure that all patients can access appropriate treatment. We also develop new therapeutic options through alliances with partners like DNDi, Bristol-Myers-Squibb, and Bayer Healthcare.

In 2021, we will celebrate the 20th anniversary of our collaboration with the WHO. We are deeply proud of all initiatives this partnership has led to. Since 2001, the number of HAT cases has dropped by 97 percent, more than 40 million people have been screened, and over 210,000 patients have been treated. But the disease is still killing people – so we must maintain these efforts until we put an end to the disease once and for all.

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pharmacies. We really wanted to witness the project's success," says Tarral.

An easy-access future

Although acoziborole hasn't yet completed its trials or received a regulatory green light, the partners have made plans for Sanofi to handle its manufacture, supply, and distribution – for free.

Sanofi has a long-term partnership program with the WHO to combat several NTDs, through which it provides drug donations and financial support. Neau says, "Historically, we've contributed to this partnership with medications for patients with sleeping sickness. We also support capacity-building and patient screening through yearly contributions. Acoziborole should be no different."

Tarral adds that the project also received early support from several donors. "The Bill & Melinda Gates Foundation, among a broad range of industry partners, offered donations early on that helped drive the project. Sanofi has also made logistical considerations that will help the drug reach as many affected people as possible."

The supply chain for acoziborole will be managed by the Sanofi-WHO partnership. With support from Médecins Sans Frontières, the company will ship the drug from its warehouse in France to Kinshasa, DRC. "Once the medicines reach their destination, they will be distributed to patients in the field through the National Sleeping Sickness Control Program," says Neau. "We have years of experience in the distribution of NECT and know how cumbersome and difficult it is to ship and store the drug. With fexinidazole today and acoziborole tomorrow (if approved), the logistical challenges will be significantly simplified due to the medicine's oral form."

The partners believe they are well on their way to eliminating HAT in line with the WHO's 2030 goal. But is the industry doing enough to address the wider problems NTDs cause? "We can all do a bit more," says Tarral. "It's difficult for big pharma to invest in NTD research and that's where smaller companies and biotechs can step in. They have the capacity to focus more time and resources and can work collaboratively with larger companies to make a difference."

But no one organization, government, or company can effect lasting change alone. "It is essential we work together to ensure optimal use of resources as well as to explore and implement innovative strategies for a future in which stronger local accountability is a reality," says Neau. "Importantly, we must all remain committed to improving access to healthcare for the most vulnerable people in low- and middle-income countries."

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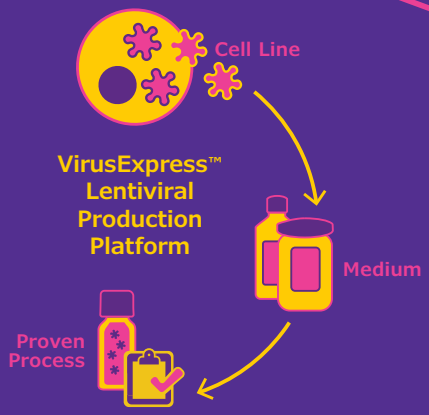

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Gene Therapy: The Rocky Road to Success

A rapid review of gene therapy's rise – and a quick glimpse into the future

By Alexandra Brinkman

The manipulation of genes to treat disease once seemed only to be the basis for an average science fiction novel. And if your story restored an individual's vision by using a virus to replace a mutant version of a gene with a healthy one, you might have a best seller on your hands. But we all now know that this is not fiction; it is a description of Luxturna, the first FDA-approved gene therapy for an inherited retinal disease caused by mutations in both copies of the RPE65 gene.

The concept of gene therapy was officially established back in 1972. And although gene therapy is considered a relatively new area of therapy, the field can be dated even further back to 1928, when Frederick Griffith first described the transforming principle. By 1968, Rogers and Pfuderer performed the first proof-of-concept viral mediated gene transfer. Fast-forwarding to 2003, China became the first country to approve a gene therapy for clinical use. By 2009, the first successful phase III trial of a gene therapy had occurred in the EU and in 2012, the EMA recommended the first gene therapy product for approval. Following on from this success, the FDA approved Luxturna, the first gene therapy for an inherited disease, in 2017 (1).

However, the road for gene therapy has not been smooth. Here, I look at genetically driven non-oncology indications, based on data from Beacon Targeted Therapies, highlighting the challenges and successes of the field.

Setbacks and successes

According to the Gartner hype cycle, a graphical representation depicting the maturity of novel technologies, gene therapy reached its peak of inflated expectation in the mid-1990s. This inflated expectation was paralleled by a rapid rise in clinical trial activity and the publication of early proof-of-concept studies for genetic conditions, such as adenosine-deaminase deficiency (ADA-SCID). It had been clear from the start that gene therapy had potential, however, focus needed to be given to the basic science of gene transfer and its respective technologies. Following this peak of excitement, the field descended into the "trough of disillusionment" following the death of Jesse Gelsinger during a clinical trial for ornithine transcarbamylase (OTC) deficiency (2). Consequently, concerns over the future of gene therapy were raised – and further

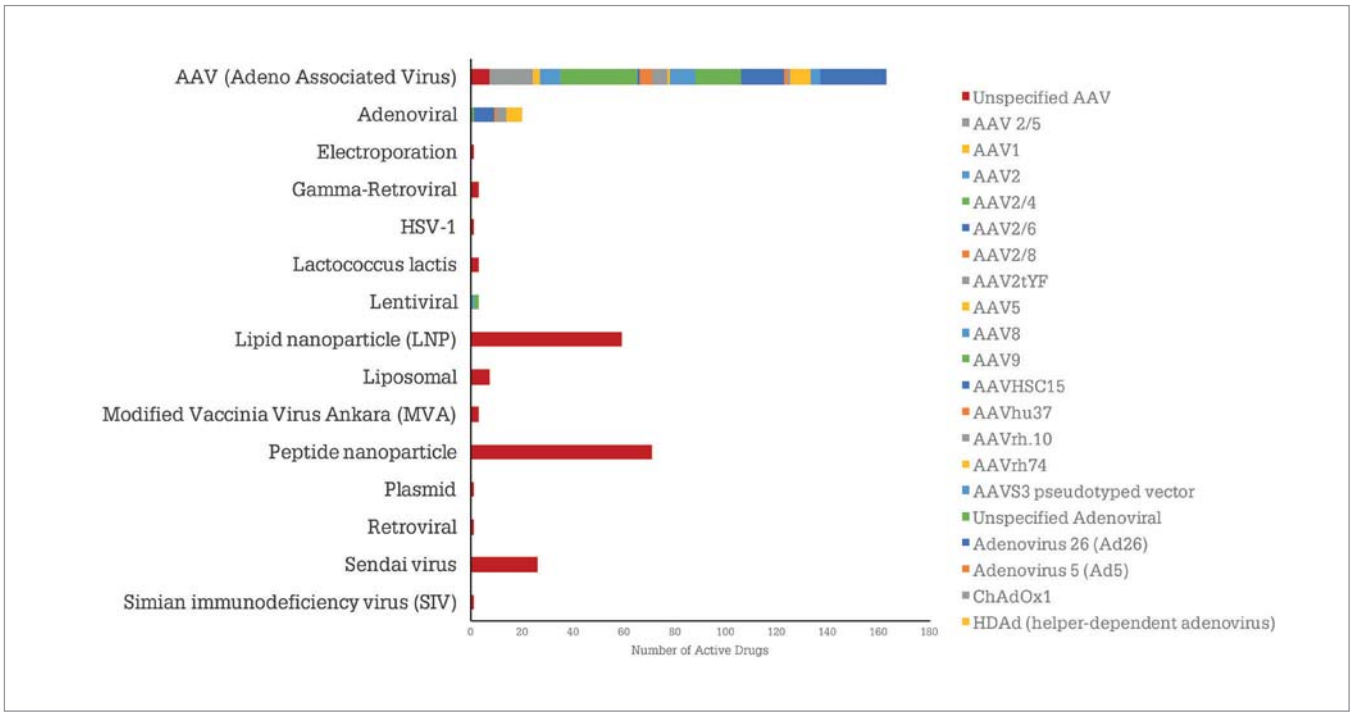

Figure 1. Vector distribution based on the number of active drugs within gene therapy. Source: Beacon Target Therapies, October 2020.

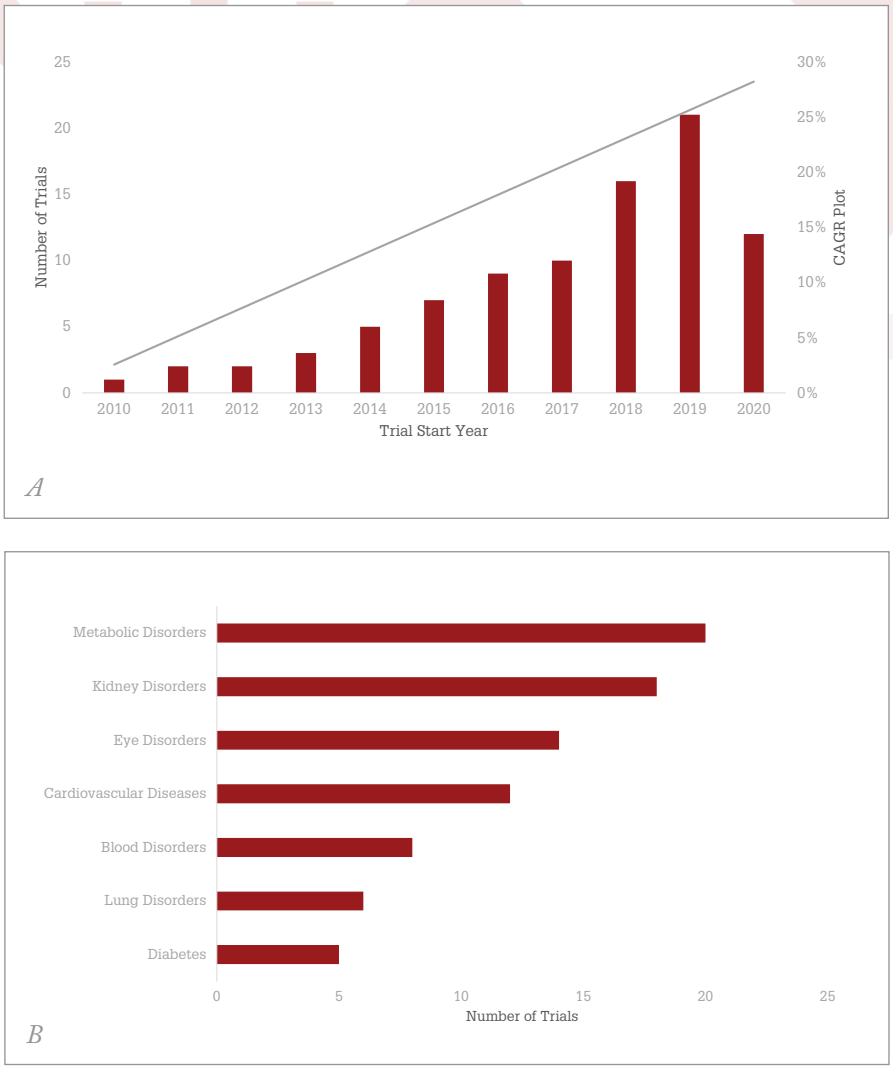

Figure 2. Clinical growth and disease variation within RNAi therapies. A) The number of trials evaluating RNAi therapies initiated per year since 2010 and the compound annual growth rate (CAGR) of 28 percent. B) Distribution of trials across disease indications, with at least five clinical trials using RNAi therapies. Source: Beacon Targeted Therapies, October 2020.

complicated by an increasing awareness of the challenges that would be encountered, including vector-induced immune response (immunogenicity) and decreased financial investment. To overcome one (possibly both) of these challenges, researchers have focused on improving their understanding of disease pathophysiology to develop safer and more efficient vectors.

The research has resulted in recent clinical successes for inherited orphan diseases from the treatment of Leber's congenital amaurosis to the EMA approving Glybera in 2012 for lipoprotein lipase deficiency (3). These successes are driving the field up what is known as the "slope of enlightenment" and into a "plateau of productivity." As a result, we've seen greater innovation in strategies addressing editing and vector technology, and the creation of more biotechnology companies dedicated to gene therapy development – backed with substantial financial investment.

We should not become blinded by the success gene therapy is having. The field is young and dynamic, but still faces challenges around transduction efficiency, clinical trial endpoints, and, most significantly, immunogenicity. As AAV vectors can be administered directly to the patient, the likelihood of a host immune response is high. Additionally, any pre-existing responses to the wild-type virus that the vector is engineered from, or the transgene product itself, can interfere with therapeutic efficacy if not identified and managed optimally. It is, therefore, important for the field to gain a better understanding of the different viral and non-viral platforms used so that immunogenicity can be minimized. Currently, the AAV vector is the most frequently used delivery system based on the number of active drugs, but also contains the greatest immunogenicity challenges (see Figure 1). Outside of AAV vectors, there are further novel vectors being created to help evade the immune response – and the clear innovation occurring in the non-viral delivery space can help to overcome the immunogenicity problems seen with AAV vectors (4).

A key challenge inherent to immunogenicity is our ability to measure and predict the immune response. A lack of standardization of regulatory protocols for assays and immune prediction levels – or, put another way, what level of an immune response is acceptable – have created problems. Patient stratification, as defined by the amount of neutralizing antibodies present, can be one alternative to help mitigate immunogenicity. It can then be decided which patients are enrolled onto trials as part of the inclusion criteria (for example, anti-adenovirus antibodies). Another strategy being used to help prevent immunogenicity is immunosuppression/patient conditioning. Though the strategy reduces unwanted immune responses to the gene therapy, there are still questions around its use; specifically, are immunosuppressants suitable for long term use? Furthermore, efficacy of the gene therapy can potentially be compromised by use of immunosuppressants. Standardization of immunosuppression protocols, such as inclusion/exclusion of use, would need to be better defined. And yet, though these are hurdles to be addressed, they have not stopped gene therapy from being validated as a therapeutic approach – and that is reflected in the present-day landscape.

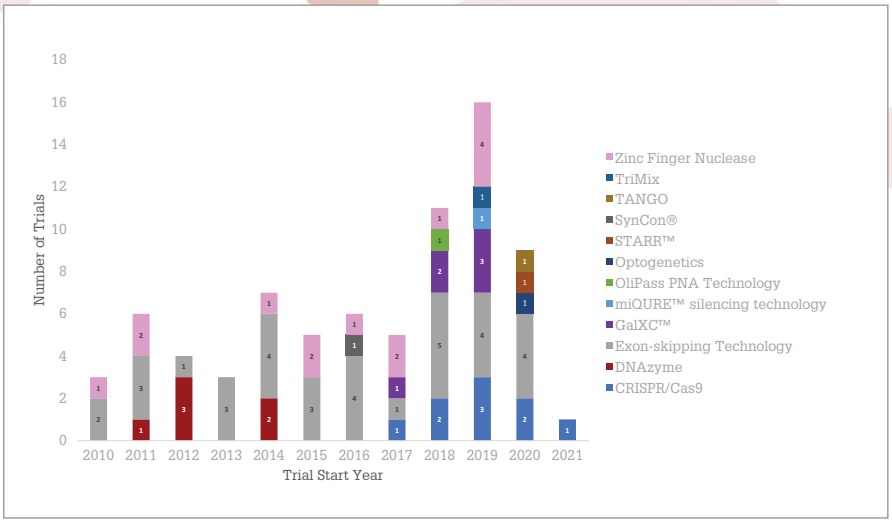

Figure 3. Number of clinical trials initiated each year in the last decade versus editing technology. Source: Beacon Targeted Therapies, October 2020.

Changing approaches

The discovery of RNAi enabled a shift from only focusing on gene augmentation and replacement to also focusing on downregulation of genes – namely, mutant variants that can result in a therapeutic effect on disease pathogenesis. This shift is reflected by recent approvals, such as Givosiran in 2019 and Patisiranin in 2018, as well as the increasing number of RNAi clinical trials over the last decade (CAGR of 28 percent) for a variety of disease indications (see Figure 2). Some of the first clinical therapies using small-interfering RNA (siRNA) were for diseases of the liver, as siRNA sequences were initially developed to target hepatocytes. Examples of this type of therapy include treatments for transthyretin-mediated amyloidosis and complement-mediated diseases (5).

In recent years, gene editing has also taken off. Gene editing tools offer a more elegant and precise method of treating genetic diseases. There have been efforts on this front through ex vivo homologous recombination, TALENS, and Zinc Finger Nucleases (ZFNs). However, clustered regularly interspersed short palindromic repeats (CRISPR)/Crispr-associated protein 9 (Cas9) has become the editing technology of choice – transforming biomedical science.

CRISPR/Cas9 started receiving attention in 2012 as an editing technique, and the first clinical trials were initiated in 2017 (see Figure 3). The tool was pioneered by Emmanuelle Charpentier and Jennifer Doudna, who received the 2020 Nobel Prize in Chemistry. Proprietary editing technologies are now rapidly being developed across the industry; for example, UniQure's miQURE silencing technology and CRISPR/OMNI.

And the future?

Although there have been setbacks, the ultimate success of gene therapy has been driven by improvements in both nonviral and viral vectors. Though the majority of assets still use viral vectors, the increasing diversity of the field is reflected in the number of nonviral assets (46 in total) that have entered the clinic for both ex vivo and in vivo gene therapy. Some of these technologies include vectors, such as cationic lipids, plasmids, and peptide nanoparticles.

Based on analysis from Beacon Gene Therapy, 88 trials are expected to be completed in 2021, with 70 trials in 2022. Consequently, an influx of data is predicted in the coming years. Looking at the number of phase III trials expected to be completed over the next five years, we can expect to see new approvals for both classical gene therapy and RNA-based approaches. Alnylam Pharmaceuticals is leading the way with three assets in phase III, but it will be exciting to see who will ultimately win the race for the next approval (see Figure 4).

According to the ARM 2020 report (6), this year (even taking into consideration COVID-19), is on track to be a record-breaking year for regenerative medicine and advanced therapy financings. Therapeutic developers raised more in the first half of 2020 than in all of 2019 (US$10.7 billion in the first half of the fiscal year 2020 versus $9.8 billion total in 2019). This year will likely provide the best year on record for cell and gene therapy financings ($13.5 billion total), with developers having already raised nearly 80 percent of the full-year total seen in cell and gene therapy financings in 2018. Investors will no doubt appreciate the robust pipeline that each of the gene therapy therapeutic classes offers; however, it is important to appreciate that, due to the immaturity of the field, there are a significant number of companies at the preclinical stage – and there will be both significant winners and losers.

It is also important to note the impact that COVID-19 is still having on the field. The increased number of INDs filed within cell and gene therapy, and a shift in focus towards COVID-19 therapeutics and vaccines, has placed an additional burden on the FDA and led to delays. For example, Sarepta Therapeutics' asset SRP-9001 for Duchenne muscular dystrophy (DMD) has seen a delay in its clinical trial. While giving late notice, the FDA has requested an additional potency assay for the release of SRP-9001 prior to dosing, resulting in trial delay. During these unprecedented times, it is likely that we will see more trials delayed while the FDA tries to keep the pace with both the increasing number

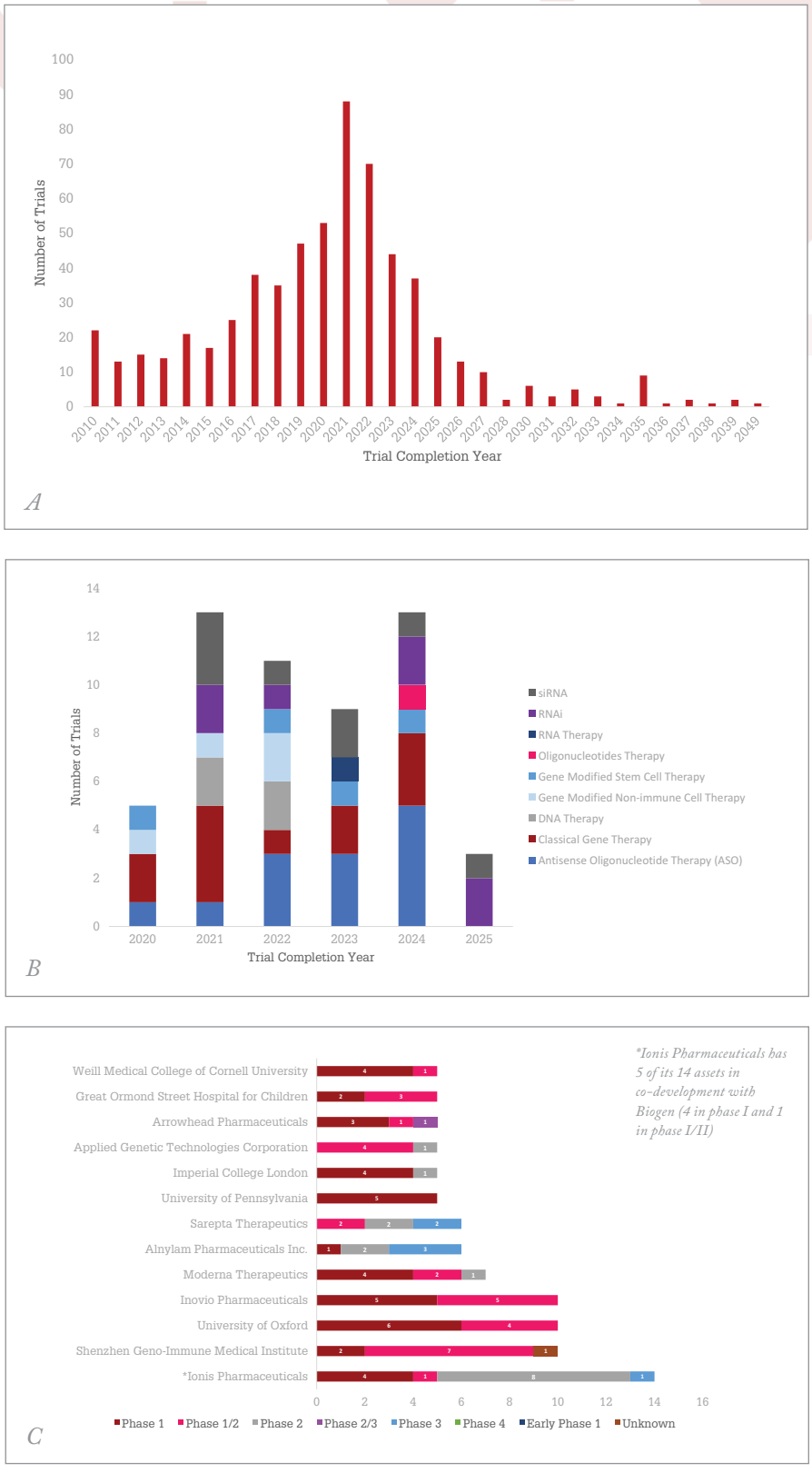

Figure 4: The Future of Gene Therapy. A) Number of gene therapy trials completed versus completion year B) Distribution of phase 3 trials coming to completion in the next five years broken down by completion year and therapeutic class C) Developer with at least five active gene therapy assets broken down by total number of therapies and highest phase of development. Source: Beacon Targeted Therapies, October 2020.

of gene therapy IND applications and the impact of COVID-19 on trial and drug development.

Undoubtedly, the path for gene therapies has been rocky. The field has seen significant setbacks, from understanding disease pathology to safety and immunogenicity concerns, but these hurdles have pushed the field to pursue improved technologies, and the variety of delivery and editing technologies available today offers a perspective on how challenging it is to tackle certain diseases. With several assets already successfully approved and more seeking approval, the approach of the field has been validated; next, we expect to see a domino effect of approvals driven by the increased influx of data, IND filings, and new technologies being implemented.

Alexandra Brinkman is a Gene Therapy Research Analyst at Beacon Targeted Therapies

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In the Face of Crisis

Sitting Down With… Elaine O'Hara, Chief Commercial Officer, Sanofi Pasteur, US (Swiftwater, PA)

How were you introduced to industry?

I moved to the US for my Master's degree in Business Administration at St. Joseph's University in Philadelphia. After completing my studies, I joined Accenture – called Anderson at the time – for a consulting role. Serendipitously, I was involved in a project that helped get Astra Merck off the ground. The newly formed enterprise had a great pipeline of drugs and was launching Prilosec, a treatment for acid reflux. I really enjoyed working with the company and decided to leave the consulting world behind. Since then, I've had the opportunity to work on many product launches. The journey has been tremendous!

What makes pharma so interesting?

It's the opportunity to intervene in public health. Though working in the industry may not be as exciting as the emergency room – and is certainly not as high-paced – I'd argue that it is still incredibly rewarding. Many people live with chronic diseases whose management requires a consistent effort on the patient's part. I've been fortunate enough to contribute to the development of a variety of interventions and witness the advances the industry has made and continues to make – positively impacting lives across the globe.

But, ultimately, it's the fact that pharma allows us to rally around the causes that really matter. The COVID-19 pandemic is one example that demonstrates how invested we are in protecting patients – but companies across the industry are also working to treat everything from CNS disorders to antimicrobial diseases. It's something we can all be proud of.

Why Sanofi?

Years before I joined Sanofi, I had already developed an interest in the company's work. It had an extensive vaccine portfolio, but what stood out to me the most were its influenza products. Once strains are identified, the manufacturing of relevant vaccines has to begin. To meet public demand, a rapid turnaround is a must. The structured timeline requires a lot of dedication, patience, and attention to detail. I wanted to be in that kind of environment and was fortunate enough to join the company in 2017. Today, I lead Sanofi Pasteur's North America commercial operations.

How has the COVID-19 pandemic affected you?

Before the pandemic began, we all met face-to-face. It was normal for me to sit down with my team and plan our commercial activities – designing strategies for the year and assessing vaccine needs across North America. That has now drastically changed. Remote interactions have become our new reality and, though it was a shock to begin with, it soon became the norm. Our sales representatives, for example, adapted very quickly. Though they had previously met with customers in physical locations, Zoom became an integral part of their continued client relationships. Beyond this, we're on track to meet many of the goals we had set at the beginning of the year. We've developed adaptive vaccination solutions that help healthcare providers immunize the patients reluctant to physically enter the doctor's office – they were concerned with exposure to the coronavirus. However, in a year like the one we've had, no one wants to see other vaccine preventable diseases cropping up. And so, it was important for us to develop solutions that supported HCPs to continue to administer all those other vaccines that protect against diseases like influenza and meningitis, these vaccines can be administered anywhere – even through the window of your car in a parking lot. This approach helps ensure that as many people as possible are properly protected against viral and bacterial infections.

Which industry figures have inspired you?

I've been fortunate in that most individuals I've reported to throughout my career have been very helpful and given great advice. It's powerful when you have a boss who encourages you to go in a certain direction and helps you grow.

Outside the industry, one of my current heroes is Anthony Fauci. He has been incredible at toeing the line with respect to what's important regarding COVID-19. He's also under incredible pressure, but he's spent years fighting for medical excellence and has a vast knowledge of pandemics, epidemics and health crises. I appreciate the work he is doing and the way he has continued to promote the scientific messages required to deal with the pandemic.

Are you optimistic about the future?

At Sanofi Pasteur, we're developing our own COVID-19 vaccine and – as our CEO put it – it's very interesting to work on a vaccine with the world's eyes on you. Internationally, people will have questions about our progress. How will this vaccine come to market? How will it be distributed? Who will receive it?

We'll be able to provide more answers as the situation changes. I think this will help the general public develop a stronger understanding of pharmaceutical products and how they are produced and delivered to the market. Conversely, there's the potential for skepticism because of the speed at which this kind of vaccine is moving through the clinical pipeline. That's something the pharmaceutical industry will have to continue to address. We have very good processes in place to ensure product safety and efficacy – but now, more than ever before, we must be able to prove that to patients.

All this being said, the public's knowledge of – and trust in – the pharmaceutical industry is better than it was in the past. Until perhaps a year ago, most people didn't have a clear understanding of what vaccine manufacturing looked like. I'm pleased that we're now at a pivotal moment where we can educate our community and reduce vaccine fear. This will help us build stronger bonds with the people we aim to serve, which can only be described as a positive step forward.

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