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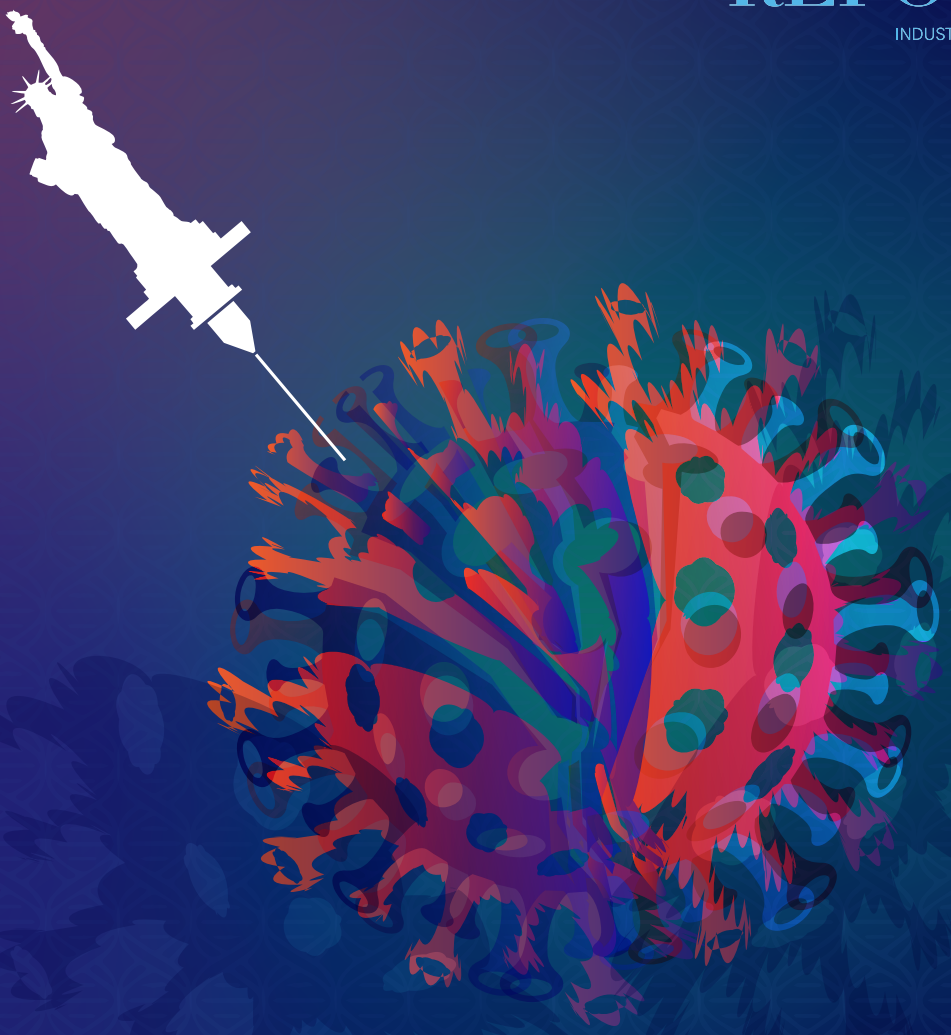

UNITED STATES PHARMACEUTICALS AND BIOPHARMACEUTICALS 2021

Drug Discovery - Covid - Funding and Investments - Contract Services
Hubs and Academia - Accelerating Pipelines - Generics

Dear Reader,

Welcome to the 2021 edition of the United States Pharmaceutical and Biopharmaceutical Industry Report.

Over the past year, the United States life sciences ecosystem faced one of its greatest ever tests in responding to Covid-19. Fortunately, thanks to years of research, development and risk taking, the industry proved up to task, and proved its remarkable dynamism. Therapeutics and vaccines were brought to market on timelines previously considered to be impossible and, at least temporarily, public opinion of the sector spiked as the industries' valiant efforts were brought to light. Beyond the headlines, companies continued to build on the progress of the previous decades, despite the many challenges Covid presented for clinical trials and supply chains. Undeterred, the industry obtained 53 novel drug approvals, across indications ranging from precision oncology to peanut allergy. With gene editing, cell-based therapies and profoundly new ways of manipulating immune cells to target cancers, today the industry has a far greater toolbox to treat disease than could previously be imagined.

With many of the great uncertainties of the pandemic now behind us, it is crucial for investors, pharmaceutical executives, manufacturers and scientific researchers involved in the US pharma and biopharma industry to remain unified and informed. The way in which groups across industry, academia, government and the broader health-care system have come together to fight this pandemic has been inspiring to many. Continuing to partner in this way will be critical in successfully navigating public health challenges of the future.

The following pages offer widespread coverage of the state of the US pharmaceutical and biopharmaceutical industry, including big pharma and its blockbuster drugs, emerging biotech and their innovative drug pipelines, and the different service providers across the value chain, from CDMOs and CROs to AI and big data platform companies. We sincerely hope that you have a great conference, full of business and networking opportunities at CPhI North America, and we hope you enjoy reading our 2021 edition of the United States Pharma and Biopharma Industry Report.

Alfonso Tejerina
General Manager and Director
GBR

UNITED STATES PHARMACEUTICALS AND BIOPHARMACEUTICALS 2021
Industry Explorations
Global Business Reports

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A Global Business Reports Publication
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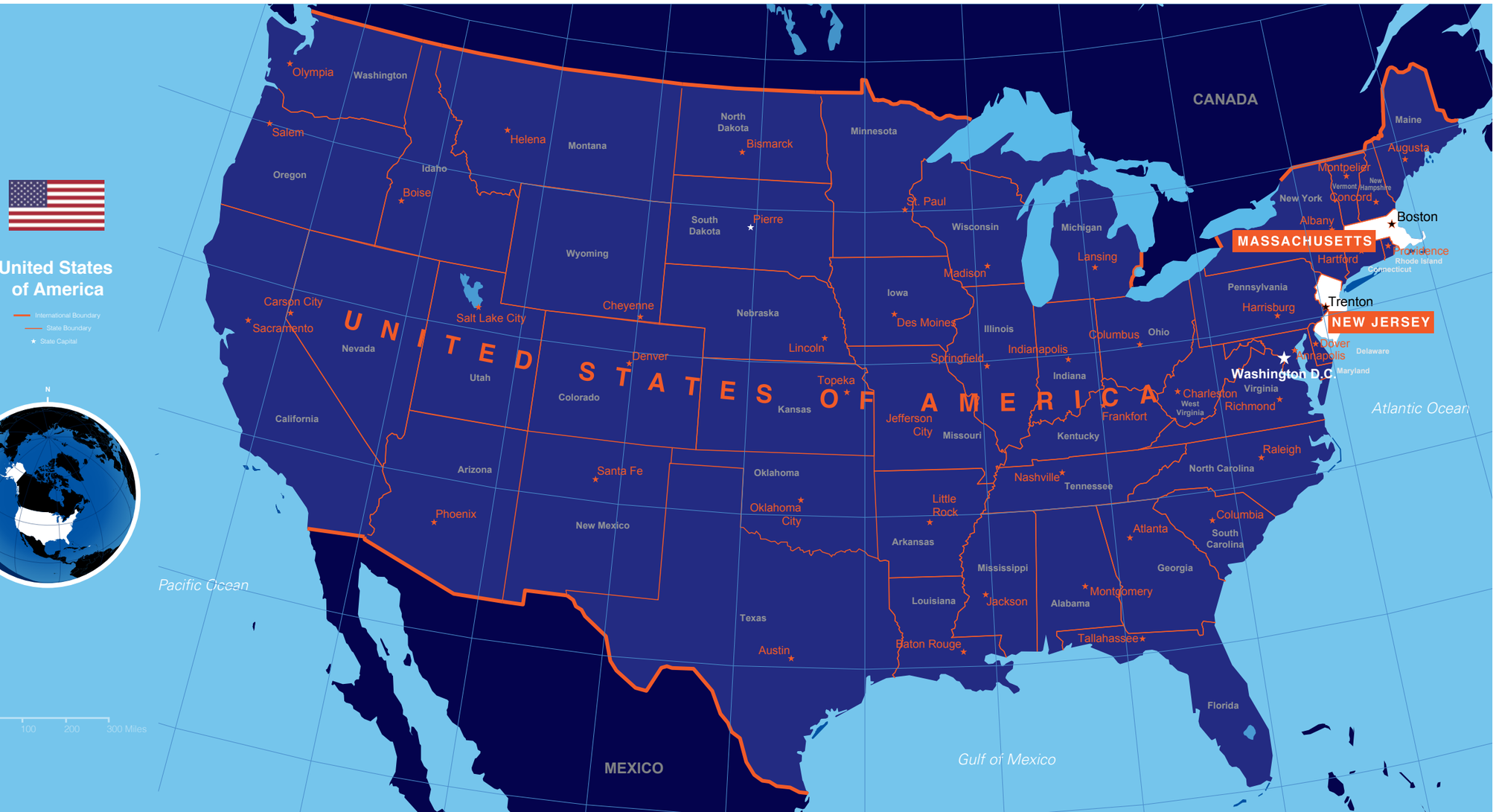

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INTRODUCTION TO US LIFE SCIENCES

"A year ago, we were telling people externally we thought that mRNA was going to become one of the biggest markets for our DNA platform, but that it needed a clinical inflection point. At that time nobody was producing at scale, but the effect of Covid-19 was that these platforms were completely validated by the efforts of BioNTech and Moderna."

- Jonny Ohlson,
Executive Chairman,
Touchlight Genetics

Image courtesy of Vedanta Biosicences / Bearwalk Cinema

Intro to US Life Sciences

INDUSTRY RISES TO THE OCCASION

Shortly after winning the Nobel Prize in Chemistry, Jennifer Doudna commented that over the course of the pandemic, she was reflecting on Thomas Kuhn's book "The Structure of Scientific Revolutions," published in 1962. It made a compelling case for "paradigm shifts," in which the accumulation of challenges to a supposed truth eventually overturns the accepted understanding of it. This seemed to explain the observation that scientific ideas and practice often bumble along for a while but then experience a rapid and substantial change that disrupts the regular way of working. Over the past year, Covid-19 has upended lives around the world, leading to over 3 million deaths as of April 2021. At its peak, the US witnessed multiple days where its daily death rate reached historical highs exceeding that of 9/11.

The sense of desperation that came out of this necessitated a rethinking of what was previously considered possible. For many years, the life science industry has had breakthrough ideas bubbling under the surface, but accepted truths are difficult to change. For example, people took it as a given that it takes years to develop a vaccine, that virtual medicine will never scale for doctors or patients, and the regulatory system cannot adapt to innovation quickly enough to support lasting change. Over the past year, the US bio ecosystem turned this orthodoxy on its head, responding heroically, and faster than ever before in so many ways. The rapid pace at which industry moved was enabled by decades of research by industry and academia, which formed the base for a mobilization never seen in the biological sciences. It rivaled the great efforts of the Manhattan Project and the Apollo moon program. The Russians even named their vaccine Sputnik, evoking memories of the space race.

In the US, the Trump administration launched its vaccine taskforce named "Operation Warp Speed," an expression popularized by Star Trek.

Coincidentally, the most efficacious and trusted vaccines that are now being administered across the US and the world are mRNA vaccines, which not long ago were considered science fiction. Even as recently as one year ago, this technology still received skepticism and lacked validation.

Jonny Ohlson, executive chairman of Touchlight Genetics, commented: "A year ago we were telling people externally we thought that mRNA was going to become one of the biggest markets for our DNA platform, but that it needed a clinical inflection point. At that time, nobody was producing at scale, but the effect of Covid-19 was that these platforms were completely validated by the efforts of BioNTech and Moderna in getting vaccines to market."

Messenger RNA is just one of several new modalities that are enabling a renaissance in biomedical progress. There are now tools for gene editing, cell therapy, microbiome, targeted protein degradation, both active site and allosteric small molecules, and even digital therapies. All of these modalities are giving the R&D community a differentiated toolkit to address distinctive conditions, which allows for tailoring and refining how we think about making new medicines.

The life sciences sector is now at a stage where the promises of cell and gene therapies are being delivered to patients; rare diseases, previously believed to be incurable, are on the precipice of real cures. Artificial intelligence (AI) and machine-learning approaches are raising expectations that therapy discovery and development may not only be more innovative, but also more time and cost effective.

The past quarter-century has seen tremendous progress in biomedical research, leading to an increasing understanding of cancer, heart disease, diabetes and other devastating diseases. The nation has led the world in such progress, due in significant part to wise investments by the Federal Government in basic biomedical research. These breakthroughs are beginning to pay off in terms of new therapies for American patients.

- Christiana Bardon, Portfolio Manager, Burrage Capital

Tech to the Rescue

Regeneron is an exemplar of many of these trends, as they were able to rapidly produce a Covid antibody cocktail leveraging their core capabilities for target discovery and validation enabled by a series of technologies that accelerate, improve and disrupt the traditional drug discovery and development process. Collectively, these technologies make up their VelociSuite platform, which played a pivotal role in treating former President Trump when he was hospitalized due to Covid in October. Robert Landry, CFO of Regeneron, outlined: "Thanks to three decades of investment in our antibody discovery and development technologies, as well as our recent experience developing a multi-antibody cocktail for Ebola, our team was ready to quickly mobilize when Covid-19 hit."

The team ultimately moved its investigational antibody cocktail against SARS-CoV-2 from lab to clinic in record time. This process, which would normally take years, was achieved in under six months.

The development of Regeneron's antibody cocktail and the fact that Moderna's Covid-19 vaccine was designed in just 48 hours is astonishing. But they are not the only ones with impressive stories. 53 new drugs were approved by the FDA in 2020 (the second most of any year), across indications ranging from precision oncology to peanut allergy, many using innovative technologies that hold the promise of uniquely impacting patient lives.

Reaping What We Sow

It should not be understated that the reason the US life sciences ecosystem was capable of responding in such rapid fashion is because of investments made decades earlier both by public institutions and private entities. Perhaps a silver lining of the pandemic is the amplified awareness by government officials and the public that the solutions in diagnostic testing, drug treatments and vaccines will come from industry as it translates basic science discoveries into safe and effective products. In a press conference this March, President Biden declared: "Back in the '60s, we used to invest a little over 2% of our entire GDP in pure research and investment in science. Today, it's 0.7%. We're going to change that."

More specifically, Biden has detailed his view that industries such as artificial intelligence, and biotech are central to sustaining America's competitive position in the world, therefore warranting increased investments in medical research pertaining to insidious diseases such as cancer, Alzheimer's and diabetes.

In addition to supportive funding to institutions such as the NIH, it is also essential that the FDA remains a priority. The FDA's relationship with biotech has been a positive force for the industry, as they have shown that if there is a severe unmet medical need, they can work productively and collaboratively to get drugs out to patients as quickly as possible. Christiana Bardon, portfolio manager at Burrage Capital, noted: "We saw the FDA perform at "warp speed" for Covid. But the truth is, they have been doing that same day job for years with respect to cancer and other severe unmet medical needs."

Robert E. Landry

Executive Vice President,
Finance and Chief Financial Officer
REGENERON

With innovative thinking and efficient, parallel track use of Regeneron's proprietary VelociSuite technologies, the team moved an investigational antibody cocktail against SARS-CoV-2 from lab to clinic in record time.

Can you provide an overview of Regeneron's core brands?
EYLEA (aflibercept) Injection continues to reach more patients in competitive eye disease markets, with its efficacy, safety and convenience setting a high bar for current and potential future entries. We are confident in the durability and continued growth of this important medicine for years to come. Annual EYLEA global net product sales reached nearly US$8 billion in 2020 (net product sales outside the US recorded by our collaborator Bayer), and US$4.9 billion in the US, still without a single price increase since its launch in November 2011.
Looking to the rest of our growing portfolio, more than 80% of our top-line growth in 2020 came from products and revenues other than EYLEA. Dupixent (dupilumab) global net product sales in 2020 (recorded by our collaborator Sanofi) were more than US$4 billion, reflecting growth of 75% versus 2019. This 'pipeline in a product' continues to reach more patients in need with an expanded FDA indication for atopic dermatitis in patients ages 6 to 11 and an FDA acceptance of our supplemental application as an add-on treatment for children aged 6 to 11 years with uncontrolled moderate-to-severe asthma, with even more room to grow as it meets its potential to transform the treatment of certain type 2 inflammatory diseases. We also made Dupixent treatment more convenient with the FDA approval of a single-dose, 300 mg pre-filled syringe.
As the foundation of our oncology portfolio, our PD-1 inhibitor Libtayo (cemiplimab) is achieving significant and steady growth with recent FDA approvals in two new indications, non-small cell lung cancer and basal cell carcinoma, in early 2021. Global net product sales for Libtayo were US$348 million in 2020, representing 80% year-over-year growth.
With 11 investigational therapeutics in clinic for a wide range of cancers, including eight bispecific antibodies, we continue to diversify our approach to oncology and are positioned to lead the next wave of immuno-oncology innovation.

What factors enabled Regeneron to play such an important role in delivering Covid-19 antibody therapeutics to market?
Thanks to three decades of investment in our antibody discovery and development technologies, as well as our recent experience developing a multi-antibody cocktail for Ebola, our team was ready to quickly mobilize when Covid-19 hit. With innovative thinking and efficient, parallel track use of Regeneron's proprietary VelociSuite technologies, the team moved an investigational antibody cocktail against SARS-CoV-2 from lab to clinic in record time. A process that would normally take years was achieved in under six months.

How does Regeneron's antibody cocktail work against new Covid-19 variants?
REGEN-COV (casirivimab with imdevimab) is a cocktail of two monoclonal antibodies (also known as REGN10933 and REGN10987) and was designed specifically to block infectivity of SARS-CoV-2, the virus that causes Covid-19. The two potent, virus-neutralizing antibodies that form the cocktail bind non-competitively to the critical receptor binding domain of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population, as detailed in Science.

How do Regeneron platform technologies drive its efficient drug discovery and development engine?
Our core capabilities for target discovery and validation are enabled by a series of Regeneron-invented technologies that accelerate, improve and disrupt the traditional drug discovery and development process. Collectively, these VelociSuite technologies represent some of the most valuable biotechnologies ever created, and aid our efforts to continuously accelerate the average timeline from discovery to drug approval — ultimately allowing us to help more patients around the world, faster.

What drives Regeneron's scientific agenda and how does it stay true to the company's scientific roots?
Regeneron was founded and has been led for over 30 years by physician-scientists – a rarity in the industry – and we apply this science-focused mentality to our work. We pursue therapeutic pathways based on our ability to see early promise through genetic or deep biologic research. From there, we have found that commercial success will follow. ■

This was particularly true in the case of Amgen's Blincyto, which was approved in under three months for pediatric Acute Lymphocytic Leukemia. "The FDA's thinking is that every day that they do not approve a drug like Blincyto there is a child who may die of leukemia," Bardon concluded.'

Positive Sentiment Meets Strong Fundamentals

Given the widespread suffering from loss and lockdowns leading to historically high unemployment, one might have expected the business climate to suffer. It did to some extent, as some clinical trials were disrupted and remote sales posed major challenges, but things quickly rebounded as the year progressed. The life sciences industry, in particular, had several tailwinds at its back; namely a wave of positive sentiment from society and investors. As clinical trials for Covid treatments and vaccines hit milestones, and people realized life would continue, the life sciences industry was praised for its innovation and bright future, driving stock market indices like the XBI to all-time highs, outperforming nearly all other sectors.
In addition to positive sentiment, the fundamentals driving the industry over the long term have not changed. These fundamentals include aging demographics, incredible innovation and the supportive regulatory environment. From that perspective, the industry is creating many new drugs, which are going to go on to be approved and will be entering into a marketplace growing in medical need. Even more exciting is the fact that we still understand a fraction of human biology, thus there is no shortage of potential for farfetched breakthroughs.
As Arda Ural, Americas industry markets leader-health sciences and wellness at Ernst & Young, put it:
"Unlike 2008-2009, this is not a fiscal crisis; it is a pandemic, and there is a lot of liquidity in the overall system."
According to EY's figures, biopharma alone, excluding private equity, possesses approximately US$1.5 trillion of liquidity to deploy. He continued: "Because of this underlying strength, valuations as evident by the S&P 500 Biotech or MedTech indexes, did not suffer at all. Consequently, IPOs and SPACs came back in a big way, and biotech IPOs are now at an all-time high."

Writing the next chapter

As we have witnessed with previous crises, Congress's positive view of pharma only lasts so long and eventually politicians will go back to vilifying the industry for its high prices and profits. Furthermore, capital markets will not always be as easy as they are today with well paved exit ramps leading to mergers and IPOs. Nevertheless, the far-reaching changes that the Covid-19 crisis has brought will outlast the pandemic and, in the long run, the US life sciences industry will positively alter the lives of many. ■

Scott Bluestein

CEO & CIO
HERCULES CAPITAL

We built up a deep network that enables us to be committed and dedicated to not just the life sciences, but also the technology verticals.

What were some of the key highlights of 2020?
The momentum around innovation, coupled with years of sound strategy, enabled Hercules to have a banner year. We had record total and net investment income. Hercules also ended the year with the strongest balance sheet we have had. We were able to complete several capital raises throughout the course of 2020, and we ended the year with nearly US$700 million of available liquidity.
On the investment and portfolio side, we also had tremendous momentum throughout 2020, and this accelerated later into the year. For the third consecutive year, Hercules ended up committing over a billion dollars of capital to the venture technology and life sciences industries. Despite a global pandemic, we had 22 IPO or M&A events in 2020, which is a strong validation of our model.
Our portfolio companies raised nearly US$7 billion of equity capital. These results are a testament to the overall strength, not just of the ecosystem, but of the companies that we are so fortunate to partner with.

What makes Hercules' financing approach unique in the industry?
We are arguably the only player that has been in this market consistently for the last 16 plus years that has achieved scale. We built up a deep network that enables us to be committed and dedicated to not just the life sciences, but also the technology verticals. We also have the unique ability to finance companies from the expansion stage of their lifecycle through to the established stage. Hercules can finance a company with a structured debt solution that ranges from US$10 million all the way up through US$200 million. That gives us a significant competitive advantage in that we can find companies early in their evolution and help them finance themselves through multiple value inflection points.

What are the principal advantages of venture debt?
Regardless of the quality of the company, there are going to be setbacks and successes. What is unique about our team is that we understand this reality and, rather than look at these financings as singular events, which is what an equity raise or a standard capital raise is, we look at them as long term financing partnerships, where we can support companies over a long period of time.
Venture or structured debt from Hercules is significantly less dilutive than a straight equity raise. Our team is not looking to manage or direct operations, we are not looking for board seats or control, we look to establish financing partnerships where we rely on the existing management team to continue to make the right decisions.

Given Hercules' domain expertise in both technology and life sciences, are you seeing a trend toward convergence of the two areas?
What we have seen over the course of the last 12 plus months, exacerbated by Covid-19, is the convergence of the two sectors. Consequently, we are doing more deals now across our platform where we bring our technology domain expertise and combine it with our life sciences team expertise. We are looking at a lot of healthcare tech companies along with traditional drug discovery and development biotech companies that are utilizing technologies as they look to pipeline expansion. We believe that having teams with expertise, not just in life sciences but also in technology, gives us a significant competitive advantage.

What is the breakdown of Hercules' asset mix? Are there certain areas the company favors?
Our focus is on building a diversified, non-correlated portfolio. We focus about 50% of our asset base on the technology vertical and about 50% of our focus on the life sciences vertical. We are also significantly diversified within each of those two core verticals, so we have exposure to drug discovery and development, therapeutics, healthcare tech, healthcare services and medical device companies. Our largest sector concentration within life sciences continues to be drug discovery and development, because it creates the best diversified risk profile from a funding perspective. Secondly this tends to be where the largest market opportunities exist. The last consideration is that this is where we think we can make the most difference because it is where our capital can be most useful. ■

Gil Roth

President
PHARMA & BIOPHARMA OUTSOURCING ASSOCIATION (PBOA)

What are some of the key pieces of legislature that are driving the CDMO business today?
We work with congressional offices to help give them an idea of what the CDMO sector is, and the role it plays not just in providing dosage forms for patients in the US, but also the vast number of jobs it is responsible for in America. We got involved in drug shortage proposals with congress and FDA, which have not yet been moved into law but may be revisited soon. We also helped with the opioid omnibus the US Congress developed and passed. In particular, even before the pandemic, there were questions about the pharmaceutical supply chain and how to secure it from a US-centric perspective. Once the pandemic hit, we had a lot more involvement with federal agencies, Congress, FDA and other bodies when it became clear that CDMOs were going to be absolutely critical to manufacturing vaccines and therapeutics that were going to help get the world through Covid.

Are we seeing the value of CDMOs expand in today's market?
With some key exceptions, the CDMO sector is largely private equity owned. The PE model is to hold companies for five to seven years and then either sell to another PE firm or merge with another company. This model has held up for decades. What we have seen in recent years is an increase in valuations, partly because the notion that CDMOs represent a pharmaceutical investment that doesn't carry the direct risk of R&D pipelines. You are getting some pharma benefits (steady demand and drug-driven growth), but without as much risk of collapse if a pipeline candidate fails. That said, you don't get the upside of those drugs succeeding and blowing up in the market, but CDMOs are getting steady revenue growth. ■

Donna LaVoie

President & CEO
LAVOIEHEALTHSCIENCE

What are the key factors for companies trying to effectively communicate with the general public?
Sophisticated investors and business development executives potentially looking to license in products have been the key audience, and most companies in the sector have been laser focused on how to communicate the scientific/technical part of their stories to those types of people. With the pandemic, an unprecedented number of retail accounts were opened and we have seen greater interest because of enthusiasm over Covid vaccine development. As a result, the character and size of the audience biotech companies communicate to have changed markedly, and it is not something companies are accustomed to. Often biotech executives struggle with how to distill their message in a digestible manner. In a post-Covid world, this will no longer work.

How does LaVoieHealthScience assist in implementing a strategy?
You cannot run your communications for investors' sake only. What you need to do is build a foundation of key messaging and positioning aligned with key audiences. That may be pharmaceutical partners, government authorities, health care providers, and all of that communication and relationship building creates value for the company.

Often failure or ambiguous data is something companies must deal with. What is the best way to handle these situations?
The number of times that we get the call after data readout and a client says, "It was a homerun. We hit all the endpoints p value of x, and we are off to the races," is very rare. Most of the time clients call to say, "We did not meet the primary endpoint, but we have seen activity at this dose level in this subset of patients." The challenge with that is public markets ask merely: Is endpoint achieved? yes or no, and what is the p value? That is how stocks trade. ■

Pricing

A QUANTUM OF INCENTIVE FOR A QUANTUM OF INNOVATION

Although the heroic actions of the biopharmaceutical industry granted it a temporary reprieve from intense scrutiny on pricing, it is sure to return as influential leaders on both ends of the political spectrum in the US find it politically advantageous to capitalize on people's general low regard for the industry.

We often hear the phrase "sky-rocketing drug prices" in the media and from policy makers, but the data shows this is not the case. In fact, work done by the Drug Channels Institute reveals net drug price increases have been on the decline and in single digits for the last six years. This includes innovative as well as generic drugs, despite the outliers we see from time to time.

Pharma is a popular target, because out-of-pocket costs to individuals are high relative to the rest of the world. US consumers spend roughly three times as much on drugs as their European counterparts, and 90% more as a share of income according to a report from University of Southern California. Calculations suggest that the US market accounts for 64 to 78 % of worldwide pharmaceutical profits. These profits drive the cycle of drug innovation that ultimately benefits patients around the globe.

This is frustrating to many, but the solution is not to lower US revenues. RA Capital's Peter Kolchinsky has done work elucidating the fact that this would alter net present value (NPV) calculations, potentially turning them negative, and in that case, innovation would cease. Therefore, it is important to get other countries to pay more. Until then, EU countries are like bad roommates, merely pitching in. Since every bit of revenue helps, you do not want to turn them out (ie refuse to sell them drug), but if you insist on them paying the same, they will leave (ie deny their citizens access).

The reason the US biotech landscape is so fertile and well funded is because there is that willingness to pay. Michael Kauffman, who co-founded Karyopharm Therapeutics along with his wife, Sharon Shacham, remarked: "The fact of the matter is that it is great that the US reimburses drug prices at the levels they do because without that engine we would not have such a robust biotechnology and pharmaceutical industry. We cannot do the kind of work we want to do if we do not get sufficient return on the successful investments to continue to work."

The fear around imposing price controls as proposed in HR 3 is that it will stymie innovation. The Department of Health and Human Services has calculated that legalizing importation would shave only 1% to 2% off the nation's collective pharmaceutical bill, but the bill could result in investors being less willing to pursue drug development for diseases in areas where there have been many historic failures. For instance, pancreatic cancer is a devastating diagnosis for which we need breakthrough drugs; but because the historical probability of success is much lower than in other areas of oncology (per BIO, a drug for pancreatic cancer entering Phase 1 trials has only a 1.1% chance of approval), investors would need to know that a drug that shows needle-moving efficacy would be reimbursed at a higher price than the average cancer drug.

Increasing Transparency

Calls for price controls come on the back of already increased scrutiny over price transparency. Porzio Life Sciences LLC, a provider of compliance software for transparency reporting, has unique insight into this push from state and national governments around the world. John Patrick Oroho, the company's executive vice president and chief strategy officer, observed that states have become increasingly strict in requiring transparency around prices, such that they want to see if a pharma company increased its price more than a certain percentage in a given year. Today this trend continues to grow stronger, as individual states in the US are requiring companies to show them how they arrived at a price for their new product. The government thinks that if they force companies to be transparent, then they will be more reluctant to engage in significant price increases.

Because of these more stringent dynamics biopharma companies increasingly want to diversify their sources of revenue and they want to do it earlier than they did before. "In the past, most companies always went for approval in the US, and then launched their product first in the US. Only once it was up and successful in the US after a number of years would you seek approvals elsewhere around the world, because the US provided your best opportunity to recoup all the money you put into R&D. Now, with controls around price increases and requirements for price reductions or price controls, you are starting to see parallel approvals. Companies launching their first drug are seeking approval in the US, and also seeking approval in various countries elsewhere in the world," explained Oroho.

In our Boston study we showed that patients were spending 37% less time in the clinic, and their disease progressed for 30% less time. That means less doctors' visits, less clinic time and less progression. Different countries put very different values on that

- Michael Kauffman, Co-Founder and Former CEO, Karyopharm Therapeutics

Distribution inefficiencies

One of the key problems with the system is that affordability is a function of out-of-pocket costs imposed by payers and premiums are impacted by net drug prices. The manufacturer of a drug establishes the drug's list (gross) price, which is called the Wholesale Acquisition Cost (WAC). A drug's net price equals its list price minus rebates as well as such other reductions as distribution fees, product returns, chargeback discounts to hospitals, price reductions from the 340B Drug Pricing Program, and other purchase discounts. Negotiated and statutory rebates to third-party payers, however, are the largest and most significant components of gross-to-net price differences.

Consequently, brand-name manufacturers earn substantially less revenue than drug list prices imply, due to the gross-to-net difference between a manufacturer's list and net prices.

To address this issue of therapeutics distribution, Signet Healthcare Partners CEO James Gale suggests: "We should consider the allocation of the final consumer price to the various parties in the supply chain. There is enormous waste in the money being paid to distributors, retailers, PBMs and other intermediaries. It is not sexy, but a major solution to lowering US drug costs is in improving these intermediation costs. We should ask why parties who have not invested in innovation nor taken development risks are taking a big portion of the price that the consumer pays."

Improvements in this area would also make manufacturing within the US more competitive. From Nivagen Pharmaceuticals' CEO Jay Shukla's perspective: "The issue we have is that the consumer does not see the savings because there are so many middlemen – the wholesaler, PBM, and insurance company – each getting a percentage. That is what is inflating the price, and that is putting pressure on manufacturers to operate in lower cost jurisdictions. If there were a way to either reduce the middleman's exposure, sell direct-to-consumer, or direct-to-pharmacy, then the cost of manufacturing would not be a significant factor."

Social Contract

One of the key proposals being advanced by RA Capital's Peter Kolchinsky is the idea of a social contract between patients and the biopharma industry. At its core, the proposal is about accepting that prices will be initially high on branded drugs in order to pay for innovation. But in return for paying a high price up front for drugs, companies via government legislation, will agree to allow genericization without undue delay. After a patent expires, society will enjoy the benefits of the cheap, effective generic versions for the rest of time. Similar to a home mortgage, what society pays during a period of exclusivity leads to it collectively owning a forever upgraded standard of care and longer lives. It is essential, however, that during the period in which society is paying high prices for the branded drug that insurers make appropriate care affordable for all patients.

Under this proposal a middle ground is established where the innovative ecosystem would be minimally disrupted, and society's burden of paying high prices for that innovation would not proceed beyond the duration of patents. If successful, it could go a long way in ratcheting down the rhetoric on price controls. ■

John Patrick Oroho

Executive Vice President and Chief Strategy Officer
PORZIO LIFE SCIENCES LLC

> This April, we launched our new global system, Porzio GST 5.0. It combines the US State, federal, local, and the rest of the world into one comprehensive system.

What is the fundamental problem Porzio Life Sciences' helps clients solve?
Once a company is getting close to commercializing its product in the US, they must get state licenses in order to distribute their product across the country. It can take anywhere from nine to 15 months to get all those in place. Early on, when a company is two years from their first product approval, they have an idea as to when they are going to submit their new drug application and when they plan on launching. At that time, they also have a semblance of an idea about what their distribution model is going to look like, so they are already reaching out to the major distributors, and one thing those distributors will tell them is that they can only take their product if it is properly licensed across the country. Often, the distributors will tell the company to come to Porzio Life Sciences to have their supply chain and distribution model analyzed, and to determine whether they are a virtual manufacturer or traditional manufacturer. Then they will determine what States they need to be licensed in, and what type of licenses are needed. That is one of the first areas we solve.
Once that is done, we start to get ready for interactions with healthcare practitioners. When the companies are starting to plan how to sell and market their product. They must make decisions about whether to target physicians or advanced practice registered nurses, physician assistants, and other types of healthcare practitioners. This is important because, if you have the right to prescribe a product in a particular state, the government is very interested in the type of financial interactions taking place between you and somebody who has the right to prescribe your product. At this stage, they have to put in their transparency and aggregate spend process, but also what we call their HCP engagement process. Because, if you were to just pay a physician to prescribe your product, that is a violation of the anti-kickback statute.
There are however, safe harbors and carve outs that allow you to hire healthcare practitioners who have a right to prescribe your product, and pay them for their service. There must be a documented need for the specific service, a fair market value fee and a contract specifying the services and fees to be paid. Companies must monitor and report what service the HCP is providing and how much they are being paid for such services. This legislation passed under the Affordable Care Act, and it is called the Physician Payments Sunshine Act. It is also referred to as the CMS Open Payments program.
Government agencies, investigators and prosecutors are mining the data that is reported to uncover inappropriate payments that can violate the anti-kickback statute. As a result, companies are very concerned that they are engaging the HCPs appropriately and that they are following all the rules.
At Porzio, we have been doing State reporting for life science companies in the US since 2005. Then, in 2014 we began with the nationwide reporting under the federal Open Payments program, and in 2015 we started doing reporting around the world. At that time, we had two different systems; Porzio Aggregate Spend ID, that handled the US, and Porzio GST that handled the rest of the world. As time went on, and more and more enforcement on anti-kickback and Foreign Corrupt Practices Act started taking hold, companies wanted to have a global view of all their interactions with healthcare practitioners, because they are considered high-risk interactions.
This April, we launched our new global system, Porzio GST 5.0. It combines the US State, federal, local, and the rest of the world into one comprehensive system. This software enables you to do reporting all over the world. You can see how many HCPs you are engaged with, total dollars spent, total number of transactions. You can drill down into individual countries and have a heat map or bar graphs and you can look who you are spending the most money with, be it through clinical trials, consulting work or promotional work.
We track the laws, regulations, and pending legislation for clients and then we archive all that information so that we are able to show that it has been properly done, all along.

Are there any new policies that you see on the horizon that might impact compliance?
One of the things happening both at the federal and state levels is price transparency. States are requiring transparency around prices such that they want to see if you increased your price more than a certain percentage in a given year or more than a given percentage over the last three years. Now, on top of that, there are individual states in the US that are requiring companies to show them how they arrived at a price for their new product. The companies must file a disclosure, as the product is launched. The government thinks that if they force companies to be transparent, then they will be more reluctant to engage in significant price increases. ■

Siva Samy

CEO & Chief Product Strategist
VALGENESIS

> ValGenesis makes the end-to-end validation lifecycle process 100% digital, reducing validation cycle time by over 50% and thus, helping life science companies release their products to market more quickly.

What are the key problems ValGenesis is solving for customers?
Validation is a key lifecycle process for the life science industry before releasing systems for production, commencing with system assessment, authoring requirements and risk assessment, authoring test cases, creating trace matrices, executing test cases, implementing change management, performing periodic reviews, and ending with the retirement process. In life science companies, validation is predominantly a paper-based, manual process compared to other processes that are automated and digitized, whether they be laboratory information management, quality management, or enterprise resource planning. Validation is complicated, messy and error-prone when managed manually as a paper-based process, leaving islands of data in different formats, and resulting in huge compliance risks.
ValGenesis manages each of the validation lifecycle stages as a module and connects the dots that flow data from system assessment and author requirements right up to the retirement stage. ValGenesis makes the end-to-end validation lifecycle process 100% digital, reducing validation cycle time by over 50% and thus, helping life science companies release their products to market more quickly.

Are there Case Studies of how clients have integrated ValGenesis software into their workflow?
A U.S. site for global biotechnology manufacturing and product supply operations had its validation documents and change control requests associated with several key products being approved by stakeholders across company sites in the US and Europe. The department was facing many challenges commonly associated with paper-based validation. The work eventually got done, but with more manual effort, duplication, and time than necessary, given the technologies available.
The company sought a digital validation solution that could deliver similar ROI improvements that it had come to expect from other enterprise systems such as ERP, DMS, LIMS, and MES. It needed a forward-looking approach that would eventually lead to 100% electronic validation lifecycle management.
ValGenesis was configured to meet more than 95% of the company's requirements out-of-the-box and was implemented, validated, and put into production in 12 weeks. ValGenesis offered the ability to migrate from paper toward 100% electronic validation. The project-level implementation was deemed a success based on efficiency improvements, eliminating non-value-added activities, and enabling consistency.
One year later, the department implemented an additional ValGenesis module to manage change control as a closed-loop process with validation. Through this upgrade, users could create their process flows and descriptions to capture the required justification for changes made within a validated system. Within the next twelve months, the ValGenesis solution was extended to a global biologics' development division for validation documents required in a state-of-the-art manufacturing process for new products and a supply center in Europe.
ValGenesis today streamlines the validation process for more than 3,000 users across five global company sites. Real-time access to validation documents and data enables various stakeholders to achieve compliance collaboratively and efficiently.

What are your observations in terms of the pace of cloud adoption amongst life science companies?
Life science companies have always been more conservative when it comes to the adoption of cloud technologies. These companies with fears about data privacy, data and IP protection were in the habit of purchasing a commercially available software system, installing it in their internal servers, and managing it in compliance with a corporate IT strategy and a set of standard operating procedures. Aside from the development of the software package, everything else is owned, managed, and maintained by the internal IT staff of the company. This results in high overhead costs to the company. The expense and capital burden of the on-premise model in many companies takes a back seat to the inherently slow pace of deploying functionality to the business.
The cloud business model changes the game significantly. True multi-tenant cloud computing-based systems can deliver significant value by sharing infrastructure and software across several customers. Pre-pandemic, some leading life science companies had started their digital transformation pursuing cloud-enabled capabilities with clinical trials and data science. But the current pandemic has now created an inflection point in digital adoption and technology-led business transformation.

What role has ValGenesis played for clients working remotely during the pandemic?
Technology has advanced to provide new platforms to manage manufacturing and validation processes remotely. With the help of the ValGenesis platform, our clients can now manage the validation process remotely or with limited onsite resources, without any disruption to their supply chain. ■

INDUSTRY HUBS

"The outbreak of Covid-19 challenged us to rapidly innovate and continuously iterate to address the pandemic and its far-reaching impacts, and Massachusetts led the way in developing tests, therapies, and vaccines that have helped combat the virus"

- Kendalle O'Connell,
President and COO,
MassBio

Image courtesy of CordenPharma

Massachusetts

Source: MassBio

50+ biotech companies, WPI, UMass-Worcester, and 16 other colleges

50+ biotech companies, 2 million+ s.f. in lab space, UMass-Lowell and 11 other colleges

NORTHEAST

WORCESTER

250+ biotech companies, the top 4 NIH-funded hospitals in the U.S., and 48 colleges

BOSTON
CAMBRIDGE
CORE

NIH funding US$3.711 billion, 35.2 million square feet, (according to CBRE)

WEST

Home of UMass-Amherst and 21 other colleges. Area known as **The Knowledge Corridor**

128/SUBURBS

The immediate western suburbs include 75+ biotech companies, 15 colleges, 3 million s.f. of lab space

SOUTHCOAST

Strong med device and biopharma manufacturing capacity, with numerous land sites in BioReady communities and 10 colleges

#1
REGION
for NIH Funding

New Jersey

Source: Choose New Jersey

Quest Diagnostics
Catalent
Allergan
Quintiles
Stryker Orthopaedics
Ferring
BD
Bayer Healthcare
GlaxoSmithKline
AbbVie
Daiichi Sankyo
Parexel
Frontage Laboratories
Cambrex Corporation
Pfizer
Pfizer
Novartis
GlaxoSmithKline
Valeant
Biotrial
Zoetis
Merck
Celgene
Janssen
Daiichi Sankyo
Amneal
Eli Lilly
Roche
PTC Therapeutics
Catalent
Pfizer
Allergan
Novo Nordisk
Bristol-Myers Squibb
Dr. Reddy's Laboratories
Johnson & Johnson
Sandoz
Covance
Parexel
Bristol-Myers Squibb
Otsuka
Aurobindo
Janssen
PPD

PHARMACEUTICAL AND BIOTECH CLUSTERS

#2
REGION
for NIH Funding

Introducing The Hubs

REMOTE WORK COMPELS NEW PERSPECTIVES ON CLUSTER

We all know the cliched stories of friends who have moved away to pursue their dreams: actors head to Hollywood, bankers to New York City, and winemakers to the vineyards of Sonoma. The life sciences version of this is to head for Cambridge, the Bay area or back where it all began with JNJ in 1866 in New Jersey. In theory, more open global markets, faster transportation and virtual communication should diminish the role of location in competition. Afterall, the industry just had one of its most productive years ever despite large portions of staff operating remotely. But if location matters less, why, then, is it true that the odds of finding a world-class biotech company in Boston are much higher than in most any other place?

America's biopharma industry is dominated by clusters; critical masses in one or a few places of unusual competitive success in particular fields. This teaches us that, paradoxically, the enduring competitive advantages in a global economy lie increasingly in local things, like knowledge, relationships, motivation, that distant rivals cannot match. By being in close proximity, it promotes both competition and cooperation.

These clusters in New Jersey, Boston and the Bay area, combine a unique blend of biomedical science, venture capital, entrepreneurial talent, risk-taking culture, and geographic density. Other regions have some or all of these elements, but not in the same magnitude or with the same momentum. Post-Pandemic, however, it could be the case that the gap is narrowing. An egalitarian trend toward greater dispersion of life science business activity has gained momentum as remote work has taken hold. This prompted some to seek out areas with lower cost of living, ostensibly higher quality of life and lower taxes. James Sapirstein, president and CEO of Florida-based AzurRx BioPharma, expressed his view on this trend, noting: "AzurRx is a small company, and we never felt it had to reside in the most expensive area in the country. In the biopharmaceutical industry, the feeling has always been that companies need to operate in the "biotechnology hubs" in and around Boston or San Francisco, because that is where the talent is, as well as university partnerships and venture capitalists." He continued: "VCs like to have the management teams running their portfolio companies located in the same cities as their own offices. Private equity does not feel that way, and certainly retail investors do not feel that way. Therefore, I think VCs will back off of the traditional model now that they see companies that are highly functional working remotely."

As a result, Sapirstein believes that companies will start gravitating towards tax-free geographies, such as Florida and Texas. While anecdotes of people fleeing big cities for sunnier skies are pervasive, biopharma is not an industry that can be easily moved from one place to another. In fact, it can be argued that the pandemic validated the importance of being in these clusters. According to MassBio, Massachusetts led the way in developing tests, therapies and vaccines that have helped combat Covid-19. More than 95 life sciences companies with a presence in Massachusetts have been involved in this effort, many of which are the small and emerging biotech companies that make up the backbone of the cluster. Because of the robust startup community developed around Cambridge, 18 of the top 20 big pharma companies have a presence in Massachusetts. Kendalle O'Connell, MassBio's president and COO, pointed out: "We are seeing unprecedented levels of collaboration between biotech companies and large biopharma organizations, which MassBio is dedicated to facilitating. One of the first Covid-19 vaccines was borne out of a partnership, and we believe that new ways of connecting early-stage companies with established biopharma organizations will accelerate science and improve patient lives."

Similarly, in New Jersey, of the over 800 different programs addressing Covid, 70 are being developed by companies based in the Garden State. The first FDA-approved saliva test was developed early on by Rutgers University, and Pfizer, which has a large presence in New Jersey, delivered the first vaccine – with additional vaccines coming from legendary New Jersey companies including J&J, Sanofi and GSK. There were also scores of smaller companies, such as OncoSec working on a vaccine, with Soligenix, Insmed and BioAegis all working on their own contributions to addressing the coronavirus and many others like them. Additionally, 40% of all new FDA approvals in 2020 came from companies with a footprint in New Jersey.

BioNJ founding president and CEO, Debbie Hart, commented: "Known for our strong presence of big Pharma, including 8 out of top 10 R&D companies, incredible talent pool – with 27,000 life sciences graduates each year and the world's highest concentration of scientists and engineers per square mile – and our vigorous ecosystem, fostered by Government support, world-renowned research universities, leadership in the area of cell and gene therapy and advantageous location, life sciences companies continue to be attracted to New Jersey."

On the manufacturing front, President Biden's preference for prioritizing manufacturing in America also stands to benefit New Jersey, as it is home to approximately 139 biomanufacturing facilities. Already, and late in 2020, Governor Phil Murphy signed the Economic Recovery Act of 2020, which includes an incentives package of new and revised programs to support innovation industries, such as biopharma.

John Huang, CEO of TheWell Bioscience, a biomedical technology company that helps scientists build a robust 3D microenvironment that can closely mimic the natural extracellular matrix for multiple 3D cell models such as organoids, tumor spheroids and cell co-culture, believes New Jersey to be an ideal location for a company such as his: "New Jersey provides a unique opportunity to establish an excellent industrial network. Geographically, New Jersey is ideal, as it connects to many biotech hubs and resources. We have made great connections in the area, and the driving distance to clients is reasonable. New Jersey has a great talent pool to take advantage of with many great universities in the area.

Image courtesy of Adare Pharma Solutions

ever. McCready elaborated: "When you take a look at Greater Boston, without batting an eye, you will likely end up paying somewhere in the neighborhood of on average US$90 triple net, rent per foot for lab space. In Raleigh Durham or suburban Maryland, you end up paying two thirds of that, somewhere in the neighborhood of US$55 to $60 per foot. In Austin or Dallas, you pay somewhere in the neighborhood of US$40 per foot. The equation becomes interesting, however, when you start to account for things like value."
The questions here are do you gain access to the same venture capital pool in Austin that you gain access to in Boston, and will you have access to the same amount of intellectual capital being generated? Many would argue the answer is no. "We had US$7.1 billion of venture capital invested in the life sciences in Massachusetts, and only US$1.5 billion in Texas, a state 20 times as large with 5 times the population. Furthermore, while there are a handful of great universities in close proximity to Dallas, there are over 100 colleges and universities within a 20-mile radius in Greater Boston," said McCready.
With that information, the decision to move away from the traditional clusters becomes more nebulous. As a result, decisions on where to locate are a multivariate equation which will have to weigh cost, rental price, access to venture capital, access to skilled labor, intellectual capital, support services, and political predictability in making location and growth decisions.

The state also funds attractive incubator and accelerator programs. Starting off in an incubator space has helped the company significantly with resources, consulting, connections and funding opportunities."

Talent is the greatest natural resource

In addition to the spike in remote work due to Covid, one of the big reasons people are speaking of Massachusetts and California losing their hegemony in the life sciences is because of high costs. The places that are best positioned to pull business away from these areas are in the second tier, that includes New York, Raleigh Durham, and the Maryland Mid Atlantic area. However, JLL's Travis McCready sees a compelling third tier. Places like Chicago, Los Angeles, Seattle, Austin, Houston and Dallas are all communities that have great research capabilities, access to capital, workforce training, PhDs, respect for science in the workforce, and lower cost. He asserts: "coupled with broader migration trends happening in the US, these new upstart locations have become attractive and in high demand for some developers, tenants and landlords."
There are many different ways of thinking about costs, how-

Cluster Creation

The success of the US clusters is so noteworthy that other parts of the world have launched initiatives to develop their own. The pandemic has also acted to accelerate the need for countries to have a more self-sufficient biomedical system. In Saudi Arabia, SaudiVax was established with a US$50 million grant from the Crown Prince to build a facility that will have high capacity and be able to supply a good fraction of the country's vaccine needs along with the needs of the other Organization for Islamic Cooperation countries, which consists of about a billion people. Donald Gerson, the company's COO and co-founder, described the opportunity, observing: "It was very apparent to me from global vaccine distribution that the Middle East was grossly deficient in manufacturing, was highly dependent on outside sources, and had no ability to respond to a pandemic. We thought that Saudi had enough capital to do it, and certainly enough smart, well-educated young people, therefore making it a great place to start a vaccine business."
The company located itself on the campus of King Abdullah University of Science and Technology (KAUST) and has put a Bio-Park on the university campus. "This will lead to increased availability of existing vaccines and biopharmaceuticals, and also to the development of new biological products that specifically meet regional needs. We and others in the Bio-Park intend to produce vaccines, protein biopharmaceuticals, cell therapy, gene therapy, and mRNA-based vaccines and therapies," said Gerson. ■

Debbie Hart

Founding President & CEO
BIONJ

The first FDA-approved saliva test was developed early on by New Jersey's own Rutgers University, and, BioNJ member Pfizer, that has a large presence in New Jersey, delivered the first vaccine.

How has BioNJ evolved and adapted to continue offering support and high-level discourse among its member companies?
At our very core nothing has changed and BioNJ remains passionate about helping our members help patients. We strive to ensure that New Jersey has a robust life sciences ecosystem where innovation is supported and patients can access that innovation.
However, if you drill down a bit, a lot has changed because of Covid. We have reinvented ourselves to adapt to the new "norm" to ensure that our members have the tools they need during this unprecedented time and that they are able to continue to do the work that is transforming the lives of patients around the world.
Over the last year, BioNJ has continued to support our members in numerous ways, from creating Covid-19 vaccine toolboxes, continuing our policy work in both Trenton and Washington (although virtually), to developing platforms and programming that foster engagement, mentorship, partnering and learning. We continue to build upon our Purchasing Consortium, which allows members to save money on important services and have hosted webinars specifically around Covid, such as "HR", "IT/Cybersecurity", "Finance" and the "Value of Medical Innovation" in the Age of Covid.

In what way has the industry in New Jersey responded to the challenges of the pandemic?
Globally, the industry has stepped up with lightening speed. At this point, there are over 800 different programs that are addressing Covid – whether therapies, vaccines, testing, etc. More than 70 of these companies are based in New Jersey. Many are working on more than one Covid program.
The first FDA-approved saliva test was developed early on by New Jersey's own Rutgers University, and, BioNJ member Pfizer, that has a large presence in New Jersey, delivered the first vaccine – with additional vaccines on the immediate horizon coming from legendary New Jersey companies, including J&J, Sanofi and GSK, not to mention the scores of smaller companies.
Fortunately, right out of the gate, New Jersey Governor Phil Murphy declared that lab workers were essential workers.

Has there been a silver lining coming out of the Covid challenge?
One of the silver linings has been that the capital markets for the life sciences industry have been extraordinary. Additionally, a number of the changes such as the use of Emergency Use Authorizations, expedited clinical trials and the use of data have proven to be critical to bringing Covid treatments to market. Hopefully, these policy and process changes will be continued post Covid.
In terms of manufacturing, President Biden issued a policy that is rewarding manufacturing nationally. New Jersey is in a great position to take advantage of this as we are home to approximately 139 bio-manufacturing facilities. Furthermore, late in 2020 the Governor signed the Economic Recovery Act of 2020, which includes an incredible incentives package of new and revised programs to support innovation industries, such as biopharma.

With respect to incentivizing development, what are the policies that you would want to see implemented?
The Economic Recovery Act of 2020 is the most meaningful of its kind for the industry in New Jersey's history. The programs under that legislation are in the process of being implemented, and they will have a significant impact on growing many of the companies that are currently here, and in attracting additional industry to New Jersey. Under Governor Murphy's leadership, The Hub – a new collaborative site in downtown New Brunswick featuring research, entrepreneurship, innovation and start-up incubation – represents the latest opportunity to build on New Jersey's strengths in the life sciences. Bringing the public and private sectors, along with academia and investors, together under one roof allows for new businesses, and new jobs. In November, it was announced that Princeton University, Rutgers University, Hackensack Meridian Health and RWJBarnabas Health will be the first tenants of The Hub.
As we know, cell and gene therapy is growing globally and New Jersey has quickly become a leader with more than 25% of all cell and gene therapies in development being done in New Jersey. Just last year, BioCentriq™, the Cell and Gene Therapy Development and Manufacturing Center and Center of Excellence at NJII opened. ■

Kendalle O'Connell

President and COO
MASSBIO

Despite the economic downturn and hardship caused by the pandemic, investment in biotech companies reached record-breaking levels. We had the most successful IPO year ever, with 21 biopharma companies in Massachusetts alone raising a total of US$3.9 billion.

What were the highlights of 2020 for MassBio and the Massachusetts life sciences cluster?
2020 was both a challenging and transformative year for the life sciences industry, particularly for the Massachusetts life sciences cluster. The outbreak of Covid-19 challenged us to rapidly innovate. Massachusetts led the way in developing tests, therapies, and vaccines that have helped combat the virus. More than 95 life sciences companies with a presence in Massachusetts have been involved in this effort, many of which are the small and emerging biotechs that make up the backbone of the cluster.
Despite the economic downturn and hardship caused by the pandemic, investment in biotech companies reached record-breaking levels. We had the most successful IPO year ever, with 21 biopharma companies in Massachusetts alone raising a total of US$3.9 billion.
Because of Covid-19, everyone in the world understood what it meant to live with an unmet medical need. Our industry's ability to deliver solutions to this crisis – while continuing to develop life-saving interventions for other diseases – is extremely meaningful and serves as a testament to how passionate our employees are about science and research.

How has the strength of the Massachusetts life sciences cluster enabled progress in the fight against Covid?
One of the most unique elements of the Massachusetts cluster is the robustness of the small and emerging early-stage innovation network. Nearly two-thirds of MassBio's 1,400+ members have less than 50 employees. From the lens of Covid-19, a significant portion of these small and emerging companies are continuing to innovate to not only address the pandemic today, but to ensure we have the tools to combat other effects of Covid-19 and any future health crises for years to come.
We are also seeing unprecedented levels of collaboration between biotech companies and large biopharma organizations, which MassBio is dedicated to facilitating. One of the first Covid-19 vaccines was borne out of a partnership, and we believe that new ways of connecting early-stage companies with established biopharma organizations will accelerate science and improve patient lives.

From a policy perspective, are the incentives still there to attract life sciences companies to Massachusetts?
Absolutely. On the heels of the 10-year, US$1 billion Life Sciences Initiative passed in 2008, Governor Baker passed a five-year extension in 2018 with over US$600 million in funding budgeted to drive continued growth of the life sciences in Massachusetts, including various incentivizes administered by the Massachusetts Life Sciences Center. The pipeline of start-ups we continue to see emerging in the cluster and joining MassBio is indicative of how desirable the cluster continues to be for the industry. Every five years, we conduct a strategic report that defines the future direction of the Massachusetts life sciences ecosystem and informs our economic development initiatives. Our most recent report, released in June of 2020, found that the lack of affordable office/lab space and efficient transportation posed a challenge to the cluster's continued growth. At MassBio, we are focused on addressing these issues, while also looking to build capacity across the state – particularly for biomanufacturing capabilities. Another key opportunity for Massachusetts is to expand its R&D footprint beyond oncology and rare diseases. Additionally, we want to ensure that the cluster is the best place in the world for the convergence of biotech, medical devices and digital health, and we are working to focus on how Massachusetts can do more to recruit talent and drive investments in digital health. Our goal is for Massachusetts to become a one-stop-shop for the life sciences industry.

How is MassBio working to encourage tangible progress in the area of diversity and inclusion?
For the life sciences industry to realize its true potential, our workforce must represent the patient population we serve. Accordingly, we need to identify, support, and invest in diverse leaders from across the globe. However, to achieve results, we need executives and decision-makers from across the industry to commit themselves to improving ED&I in their organizations. That is why MassBio issued our Open Letter 2.0 - The CEO Pledge for a More Equitable and Inclusive Life Sciences Cluster in the summer of 2020 and called on CEOs from across the life sciences to pledge their name to a set of best practices to implement meaningful change in the industry. As of February 2021, 213 CEOs that represent the breadth of the life sciences industry have signed the pledge. ■

Travis McCready

Executive Director
US Life Sciences Markets,
JLL

There is dramatic and intentional growth in development of biomanufacturing infrastructure in all of the research nodes across the US.

Can you provide an overview of JLL and the services it provides to the life sciences industry?
Some of the hurdles and barriers of getting from early-stage translational research to commercialization in a product are real estate related issues, and they can be sources of significant cost, lack of efficiency, and lack of coordination. From an engineering standpoint, these properties are highly technically specific, and JLL has the services, expertise and knowledge to help streamline the development and investment in those properties. Our clients are scientists who should not have to manage the arcane dark arts of construction. We manage that for them.

How has Covid impacted work arrangements in the life sciences?
Covid accelerated three pre-existing trends. One is what we call occupancy planning. Covid accelerated this by forcing people to work from home, which made companies wrestle with how to provide employees with access to data from their experiments while at home. It also shifted how lab access scheduling works. Several of our companies are now running 24/7 lab operations in order to stagger and stack their employees' access to equipment. Trend number two is collaboration and exchange. The world would not have been able to develop a vaccine in 11 months if scientists, researchers and companies were not collaborating behind the scenes. It accelerated the notion that the unit of intellectual property is no longer necessarily just data. The unit of intellectual property is in the processes and procedures as well. We see companies, scientists and researchers across platforms collaborating in extraordinary ways. It reinforces the need for scientists to want to be near one another, in the same geography and in these innovation clusters. Covid is reinforcing the lesson that the best way to collaborate and commercialize faster is to be physically near your peer or your competitor.
The last trend is biomanufacturing infrastructure. Covid exacerbated an already tenuous manufacturing supply chain. Reshoring, as a political concept, is not new, but increasingly we see nation-states creating economic incentives to keep advanced biomanufacturing within their federal jurisdictions for both economic development and public health reasons. As applied to biopharma, this is new and will have ramifications.

To what extent is JLL observing a boom in biomanufacturing infrastructure building?
When you look at the US, you see biomanufacturing in Massachusetts, New Jersey, Raleigh Durham, Philadelphia, greater San Diego… It maps right on to where the R&D nodes are. That is incredibly exciting, but also incredibly challenging, because this real estate infrastructure does not necessarily exist in all of those locations. For years now, the life sciences industry has been investing in lab space and lab R&D. However, there has not been similar attendant investment in the development of biomanufacturing space. Now what we hear from companies is, we need that biomanufacturing space, and we need it yesterday. There is dramatic and intentional growth in development of biomanufacturing infrastructure in all of the research nodes across the US.

Do you see the importance of clusters diminishing?
For years now, there has been a hegemony in the life sciences, with Massachusetts, San Diego and San Francisco leading the way. Close behind, there is a yeasty second tier, that includes New York, Raleigh Durham, and the Maryland Mid Atlantic. The exciting trend that JLL is watching is the third tier. Places like Chicago, Los Angeles, Seattle, Austin, Houston, Dallas. Communities that have great research capabilities, access to capital, workforce training, PhDs, respect for science in the workforce, and lower cost. Coupled with broader migration trends happening in the United States, these new upstart locations have become really attractive, and frankly, in high demand for some developers, tenants and landlords.
In the end, in the life sciences, location continues to matter. Now, more than ever, firms are seeking deep insight into geographies in order to weigh cost, rental price, access to venture capital, access to skilled labor, intellectual capital, support services, and political predictability in making location and growth decisions. ■

Originating Discovery

Image courtesy of Oleg Mityukhin in Pixabay

There is a common perception that much of the research produced by academia dies in academia without ever having any practical real world application. This dynamic is now changing. America has immeasurable talent coming from its universities and, in recent years, the life sciences industry has looked to tap academia to help develop scientific breakthroughs that can be leveraged to achieve their commercial goals. Conversely, universities find industry partnerships valuable because they help advance their capacity to conduct high quality research, which can be an influential factor in attracting high level academic talent and top tier students. In analyzing each of the respective biopharmaceutical clusters throughout the US, universities are their backbone: MIT, Harvard and Northeastern University in the Boston-Cambridge areas, Stanford and Cal Berkeley in Silicon Valley, Princeton and Rutgers in New Jersey, Upenn and Temple in Philadelphia, Columbia and NYU in New York and the Research Triangle has North Carolina State, Duke and University of North Carolina at Chapel Hill. Each of these universities is world class and plays an integral role in geographically anchoring the ecosystem.

While Universities remain fundamentally about teaching, research and service, tech transfer and commercialization are often seen as the fourth leg economic development part of their missions. Despite this additional leg growing in importance, ultimately, everything a university does revolves around its primary missions. Lesley Millar-Nicholson, director of MIT's Technology Licensing Office, which sees 800 new ideas coming in the door each year, commented: "Some of it is going to translate into commercial opportunity, but the key thing for universities is that they can invest in areas that large corporations typically do not. Increasingly you see corporations coming to universities or working in public-private partnerships to advance ideas that they might have done themselves in prior years."

Princeton University's Elizabeth Adams, director of their office of Research and Project Administration, expanded on this notion of what universities can do that corporations cannot, pointing to the grant money that universities receive from government bodies. She asserts: "Investing in basic research typically does not make sense for a business. However, it makes complete sense for universities and government to do. Government and university investments in basic science have birthed entire industries that have created millions of jobs. These investments are one of the reasons why the US is a leader in technologies of the future. The private and public sectors working together are exceptionally powerful in the US, and it provides us a competitive advantage."

As a result of this transfer of risk, the relationship between venture firms and universities has also evolved in recent years. Anthony Williams, new ventures associate at the office of technology licensing, Princeton University, reasons that this reflects a desire on the part of VCs to get in very early, find a platform technology that is exciting, and build the company from the ground up, working with University researchers. In that case there is more value to be captured from the VC's perspective. He remarked: "Previously we would have been furiously trying to get these assets up to IND phase: Beg, borrow and steal to get a few dollars in to do the next set of experiments to get to the point where we might be able to attract a VC to come and look at some of our technologies. Now, we are seeing a shift… VCs recognize that it is the people that are doing the brilliant science and have the ideas that are going to be the ones that develop the next game-changing technology."

Evidence of this shift was easy to come by over the past year, as Princeton saw its biggest ever seed round in the life sciences for Nereid Therapeutics, a company Professor Cliff Brangwynne, a recent MacArthur Fellow known for his groundbreaking work in cell biology, founded alongside Apple Tree Partners, who made a US$50 million funding commitment. Coleen Burrus, director of corporate engagement and foundation relations at Princeton, added: "We are seeing the results of Princeton investing substantial resources to build the infrastructure to assist faculty interested in collaborating with industry and starting companies. The university has been very focused on this for the past six years, and we are now seeing the results of this in a big way."

Although VC dollars are helpful, the success of a university spinout can often be strongly correlated to the robustness of the broader ecosystem it exists within. MIT, for example, relies heavily on partnerships with its surrounding ecosystem. These include other universities, hospitals and corporate partners. "Many great ideas come out of MIT, but we cannot translate them without help. For the university, it is about pulling together the smarts, intellect and funding, and then finding the right partners to help translate it. One of the strengths of MIT is this ecosystem that enables entrepreneurship and translational research to occur," Lesley Millar-Nicholson detailed.

When this process of translating science into technology works well it is an undeniable boon for society and each of the respective clusters. It creates economic dynamism with an abundance of new jobs ultimately devoted to bringing world-class medicines to patients. MIT spins out over 32 startup companies per year approximately, and about 358 of those companies remain alive today. Among them are a who's who list of the top biotech companies in existence. Editas, one of the leading gene editing companies was licensed through the Broad Institute, Beam Therapeutics had a very successful IPO in 2020, Taris Biomedical, which focused on bladder cancer, was bought by JNJ last year, and Alnylam continues to bring innovation to the world through its RNAi technology.

The success of these companies illustrates that there are billions of dollars stuck in professors' minds around this world that can be tapped into. However, it is a long road toward commercialization, one that only a few clusters around the world have yet to figure out. ■

> *It is not all about money in university-industry relationships. Sometimes it is about the exchange of people, materials, confidential information or large data sets, which can be just as valuable as, or more valuable than, an exchange of money. In particular, at Princeton we are seeing an explosion of data exchange and use agreements. Data is the new IP, and it is more and more a focus of university agreements with industry.*
>
> **- Elizabeth Adams, Director, Office of Research and Project Administration, Princeton University**

Elizabeth Adams, Coleen Burrus, Dean Edelman, Anne-Marie Maman & Anthony Williams

EA: Director,
Office of Research and
Project Administration
CB: Director,
Corporate Engagement and
Foundation Relations
DE: Life Sciences,
Corporate Engagement and
Foundation Relations
AM: Executive Director
Princeton Entrepreneurship
Council
AW: New Ventures Associate,
Office of Technology Licensing
Pprinceton university


EA


CB


DE


AM


AW

What were some of the key developments and partnerships established over the past year?
CB: A highlight of the past year has been long-time Princeton professor Rodney Priestley becoming the University's inaugural vice dean for innovation. In this newly-created position, Rod leads a University initiative, Princeton Innovation, that is building awareness on campus and beyond of Princeton's support for innovation and entrepreneurship. So, for example, through Princeton Innovation, we held a large virtual conference called Engage 2020 that was open to faculty, students, our partners and the public. The goal was for everyone to learn about Princeton University's innovation ecosystem and how it helps extend the impact of research beyond campus through innovation and entrepreneurship.
AW: One of the new programs that I'd like to highlight is an engagement between Princeton University and the Wharton School of Business at Penn. The Princeton Wharton Entrepreneurship Executive Education Course provides formal entrepreneurship training. The initial course was virtual and took place in January. Over four days, the team from Wharton worked with Princeton faculty members who had either already started a company or were in the earliest stages of exploring ideas for a wide range of potential businesses.
AM: This year, we also launched Princeton Startup Bootcamp, powered by Techstars. Princeton Startup Bootcamp is a two-day boot camp in entrepreneurship for graduate students and postdocs that is led by startup accelerator TechStars and organized by Princeton Innovation. Ten teams and 45 people participated in the first instance of the new program in January 2021. After two days of workshopping, participants presented their business ideas to a panel of judges.

How has the relationship between venture firms and universities evolved in recent years?
AW: Speaking of Cliff Brangwynne, in the last 12 months, we saw Princeton's biggest ever seed round in the life sciences for Nereid Therapeutics, a company that Cliff founded with Apple Tree Partners, who made a US$50 million funding commitment. This is reflective of a desire on the part of VCs to get in very early, find a platform technology that is exciting, and build the company from the ground up, working with University researchers. We are currently working with large strategic venture funds on another big seed round for another professor in our molecular biology department. The VCs want to get in and work with our inventors from the very beginning and build everything with them from the ground up. We have seen this happen more in the last year than ever before.

What are the expectations of life science corporations when they engage Princeton in partnerships?
EA: Industry is increasingly looking at platform or master agreements with which to engage universities. These kinds of agreements typically give Princeton the flexibility to bring faculty from different disciplines to the table to meet an industry partner's needs. Master agreements also represent efficiency in that, when a match between industry needs and University strengths is established, a "pre-negotiated" contract is already in place—the collaboration can get going without delay, and the money can flow. But of course it's not all about money in university-industry relationships. Sometimes it is about the exchange of people, materials, confidential information or large data sets. In particular, at Princeton we are seeing an explosion of data exchange and use agreements. Data is the new IP, and it is more and more a focus of university agreements with industry.
DE: Companies are engaging with Princeton researchers to better understand the fundamental mechanisms and pathways that create targets and delivery opportunities for new therapeutics. Princeton's strengths in structural biology and computational biology are critical as are the tools we have available, like the latest cryo-EMs.

What function does higher education perform that industry is not willing to?
EA: Government and university investments in basic science have birthed entire industries that have created millions of jobs. These investments are one of the reasons why the US is a leader in technologies of the future. The private and public sectors working together are exceptionally powerful in the US, and it provides us a competitive advantage. ■

Lesley Millar-Nicholson

Director
MIT TECHNOLOGY LICENSING OFFICE

> **MIT spins out over 32 startup companies per year approximately, and we have about 358 companies that are still alive, so the ecosystem is functioning well.**

What role do universities play in driving innovation in the life sciences?
Universities are fundamentally about teaching, research and service, while tech transfer and commercialization are often seen as the fourth leg economic development part of the missions. Ultimately everything a university does revolves around these missions. Therefore, all of the research being done, regardless of whether it is funded by government, corporations or philanthropic organizations, is driven with the idea that students will be taught, research will be conducted and publications will be created. Ultimately, some of it is going to translate into commercial opportunity, but the key thing for universities is that they can invest in areas that large corporations typically do not. Increasingly you see corporations coming to universities or working in public-private partnerships to advance ideas that they might have done themselves in prior years.
Looking at MIT specifically, we do not have a medical school, therefore we develop partnerships with our surrounding ecosystem. Many great ideas come out of MIT, but we cannot translate them without help. For the university it is about pulling together the smarts, intellect and funding, and then finding the right partners to help translate it. One of the strengths of MIT is this ecosystem that enables entrepreneurship and translational research to occur.

How specifically does the Tech Licensing Office assist the MIT community and move ideas forward to real world application?
Every year we are seeing over 800 new ideas coming in the door. Part of our mission is to get these technologies into the hands of people that can develop them and take them out the door. Some of them are patentable while others are not. We have a staff of 50, and the licensing group has a staff of 18. We also have an essential infrastructure in terms of finance, IP, patenting, marketing and communications. About 60% of the research funding that we see comes from the federal government and about 22% comes from corporate entities. The remainder is a balance of state and other funding.
Corporate sponsors might have a specific interest and reason why they made a contract with MIT, and therefore we follow their lead. The federal requirements are driven by federal agencies, such as NSF, DOD or DOE. That is why we have a corporate and federal compliance team and we have a responsibility to report every invention that has federal funding back to the federal government and tell them what it is and what we intend to do with it. If we decide that we want to commercialize something, we have to tell them and comply with their timelines.
We predominantly license to startup companies for exclusive licenses. That tells you that the technology we are seeing is so early stage that large companies are probably not going to invest in it. For non-exclusive licenses that might be more ubiquitous, large companies can be more prepared to come along because it either needs less development or it is ready to go. Our day to day is that process of receipt of an invention disclosure, an assessment and patent filing, some marketing, working with parties who are interested in licensing it, negotiating licenses, and getting it out of the door. At the back end, we manage the licenses and any revenue that comes in. We then distribute revenue to inventors, the departments, joint owners and the university itself.

What are some areas of health related scientific research that MIT is particularly strong in?
Some of our strengths are in biological engineering and synthetic biology. People like Angela Belcher, Linda Griffith, Angela Kohler, Ed Boyden and Jim Collins are all renowned in their field. The Picower Institute, McGovern Institute, Broad Institute, and Whitehead are also seen as leaders in the field of brain research. Additionally, the work of Dan Anderson and Bob Langer in drug delivery using nanotechnologies has been pioneering. Finally, the MIT-Harvard Broad Institute has established itself as a global leader in the field of gene editing.
MIT spins out over 32 startup companies per year approximately, and we have about 358 companies that are still alive, so the ecosystem is functioning well. ■

LIFE SCIENCES INVESTMENT CLIMATE

"Some of the gene therapy and cell therapy products have proven in clinical trials now to cure disease as opposed to just addressing the side effects. Therefore, there is a paradigm shift taking place right now in the research resources being allocated."

- James Gale,
CEO,
Signet Healthcare Partners

Image courtesy of Lonza Capsules and Health Ingredients

Funding Environment

LIFE SCIENCES ENTER THE MAINSTREAM

Investing in the life sciences is an extremely risky endeavor. Less than 5% of drug discovery projects ever make it to market, and they do not fail solely on the basis of setbacks in biology. Unlike other industries, where businesses can launch a product within months, biotech companies often require years of intensive cash burning before a product can be commercialized. Consequently, most life science startups fail to cross the proverbial "Valley of Death."

While failure to adequately fund a biotech company is a persistent risk, in 2020, many of these risks were assuaged by record low interest rates, aggressive economic stimulus, and a wave of positive sentiment surrounding the importance life science companies play in delivering drugs and therapeutics that contribute to our collective wellbeing. This positive sentiment was not misguided, as 2020 showed what can be achieved by those companies that reach the other side of the "Valley." It was also a good reminder of why it is a good idea to fund multiple companies, particularly with different technologies, to tackle major unmet needs simultaneously. The redundancy is often good for patients, since we do not know a priori which approach will work best. The race for a Covid vaccine demonstrated that unleashing industry competition catalyzes progress and, in turn, more and better options for patients.

The progress and liquidity available was not limited to companies developing Covid related treatment; the light also shone on companies with pipelines targeting a wide spectrum of disease indications, from CNS disorders to Oncology. We are now amidst a monumental boom in funding for life sciences. As Peter Meath, Co-Head of Healthcare at JP Morgan Commercial Banking put it: "Covid-19 highlighted the solutions the life sciences industry can provide, and we are seeing an acceleration of innovation and investment across this space as a result. I believe this influx of capital is overdue, and a net positive for the sector."

Capital floods into public and private markets

While the biotech industry used to have a fairly clear cut funding structure, the lines are no longer so clearly demarcated. There has been an explosion of alternative sources of capital and they are manifesting in many different forms. On one end, there are retail traders buying stocks commission free on Robinhood, and generalist newcomers like Mark Cuban launching a generics brand, while on the other end of the spectrum, top-tier biotech investors like Perceptive, RA Capital and 5AM have all launched Special Purpose Acquisition Companies (SPACS) with the hope of enabling companies to access public markets in a more efficient manner.

With capital readily available, both public and private companies have a plethora of options to retool their companies and structure them for the future that lies ahead.

On the public markets side, AzurRx has transformed itself by vastly improving its balance sheet to the point where it was able to bring in a new clinical-stage asset through an exclusive worldwide license agreement with First Wave Bio. According to James Sapirstein, the company's president and CEO: "The agreement was driven by our ability to raise a substantial amount of capital in 2020 and into 2021. The asset is a micronized version of niclosamide that we are developing as a treatment for two indications - Checkpoint Inhibitor Colitis and Covid-19 GI infections."

In addition, the funding allows AzurRx to comfortably continue to advance the clinical program for its lead investigative candidate, MS1819 in cystic fibrosis.

In the Mid-Cap biopharma space, rare disease focused Insmed went through an equally metamorphic year. The company's chair and CEO, William H. Lewis, explained: "We went from a one product company with one approval in one area, to a three-program story with global reach. What is important about these programs is that each has the potential to be the cornerstone of therapy in the respective diseases they address."

The three programs referred to are for treprostinil palmitil inhalation powder (TPIP), which is a novel drug with the potential for disease modifying impact for pulmonary hypertension; Brensocatib, which is Insmed's phase three development for the treatment of bronchiectasis, for the exploitation of a new pathway for the treatment of neutrophil mediated diseases; and ARIKAYCE, the first ever approved therapy for the treatment of refractory nontuberculous mycobacterial lung disease (NTM) caused by Mycobacterium avium complex (MAC).

Accelerating Early-Stage Startups

2020 saw US$51 billion of VC investment go into the healthcare sector (biopharma, health-tech, diagnostics/tools, devices) across the US and Europe; a 47% increase in investment from 2019. By all measures this constitutes a banner year. However, as Chris Garabedian explained, it is still not an easy road for early-stage companies to navigate. Garabedian founded Xontogeny on the premise that when the large VCs close a fund, they are not starting 50 companies. Even if they have a billion-dollar fund, they are trying to put US$100 million into 10 companies. Therefore, Garabedian asserts: "While we have seen an infusion of new capital come into the space, it has not necessarily resulted in the same proportion of new companies. This means that entrepreneurs have not had many funding options if they do not 'win the lottery' by being picked by one of those VCs."

In fact, the cards might even be stacked against them, because they are not going to want to take a US$100 million series A round if it means dilution for them. For that reason, many early stage companies have eschewed the company creation model and are searching for a different course. "I started Xontogeny to have a founder friendly option, which allows our team to advise, mentor and coach. We wanted to provide a home for that true entrepreneur, scientific founder, or first-time CEO. There are a plethora of cool technologies out there, and the funding of these companies should not be dominated solely by billion-dollar VC funds," Garabedian affirmed.

One of the early success stories to come out of Xontogeny came in February 2021, as Landos Biopharma, which is focused on the discovery and development of therapeutics for patients with autoimmune diseases, filed for a US$100 million IPO. The company's pipeline is powered by its LANCE precision medicine platform, which makes predictions of immunometabolic function and helped accelerate the timeline for its lead asset, BT-11. "In four years, Landos has grown from an idea to a Phase 3-ready asset. We have a unique opportunity to take our BT-11 asset into commercialization, which has a better safety profile than any other drug used for UC and Crohn's," said Landos CEO Josep Bassaganya-Riera.

Manufacturing the Renaissance

As much as the development of life altering drugs is a triumph of ingenuity and imagination, so is the ability to manufacture them. For this reason, an increasing number of players are looking to finance CDMOs; a case in point being Arch Ventures' Robert Nelson, who founded National Resilience after Covid exposed critical vulnerabilities in medical supply chains. At the companies launch, Nelson noted: "Today's manufacturing cannot keep up with scientific innovation, medical discovery and the need to rapidly produce and distribute critically important drugs at scale."

This is the exact problem Forge Biologics is out to solve, and it is why the company attracted US$40 million in funding in 2020 to build a state-of-the-art, 175,000 ft2 cGMP facility, dedicated to AAV viral vector production. As Timothy J. Miller, president and CEO of Forge described: "2019 and 2020 saw huge inflection points in the number of gene therapies that entered clinical trials. The increased number of programs that are nearing clinical trials is a reflection of how the field has grown over the past 10 years."

Indeed, as viral gene therapy has become a mainstay approach for potentially treating patients with a genetic disease, the therapies are growing in

Image courtesy of Forge Biologics

popularity. However, scalability remains an enormous bottleneck. Miller continued: "Now, in many aspects, it is up to manufacturers to catch up as demand for gene therapy manufacturers far exceeds capacity."

Another tailwind driving CDMO growth is the continued increase in capital going into research and development for both pharma and biopharma. More startups are being funded, resulting in a larger pool of potential customers for CDMOs to work with. In addition, big pharma has been increasing its external R&D budget, so the outsourcing trend stands on solid ground. Aragen Life Sciences (formerly GVK BIO) has been one of the beneficiaries of this trend, enabling the company to grow its offerings on both, small molecule solutions from concept to commercialization, and large molecule R&D. CEO Manni Kantipudi noted that the company's cell line development business has nearly doubled over the past two years. "We are known for our work with difficult to express proteins, where customers reach out to us, after failing to achieve success either internally or with other CROs. We are now forward integrating our track record in cell line development into an investment in cell culture manufacturing, to best serve our biotech customers that prefer a single partner for both development and clinical manufacturing," said Kantipudi.

In the highly volatile world of biotech, CDMO's offer a less risky way to invest, which is why these companies are favored by private equity firms. This dynamic was evinced by Piramal Pharma Solutions (PPS) securing Carlyle Group as its growth investment partner in June 2020. Carlyle's 20% stake in the business is worth approximately US$490 million. PPS CEO Peter DeYoung commented: "We realized that we were missing a piece of our puzzle in terms of drug product in the US. As a result, PPS expanded the company's portfolio by acquiring a drug product facility in Pennsylvania, capable of delivering potent solid oral dosage forms."

Despite differences in the risk profile of biotech and CDMO businesses, the story remains one of record growth and funding across the board. "What we have seen in recent years is an increase in valuations, partly because of the notion that CDMOs represent a pharmaceutical investment that does not carry the direct risk of R&D pipelines. You are getting some pharma benefits: steady demand and drug-driven growth, but without as much risk of collapse if a pipeline candidate fails," Gil Roth, president of the Pharma and Biopharma Outsourcing Association (PBOA) elucidated.

Funding our Future

Although 2020 will certainly be anomalous in some respects, there is a clear lesson to take away from it. The American innovation system is far from perfect, but it works. Strong support for basic science is an important start, but it takes entrepreneurs, venture capital, and many other alternative sources of capital along the way to translate it. As Moderna CEO Stéphane Becnel said in describing his company's successful vaccine effort: "It was an overnight success, 10 years and US$5 billion in the making." ■

Peter Meath

Managing Director,
Co-Head of Healthcare
and Life Sciences,
Middle Market Banking &
Specialized Industries
J.P. MORGAN COMMERCIAL BANKING

> **While the underlying business model for life sciences companies has not changed as a result of our current environment, we are seeing that increased capital has been made available to those seeking funding.**

What did 2020 look like from J.P. Morgan's perspective and what are some of the initiatives the company has taken on over the past year?

In early 2020, we were bullish about developments in the life sciences sector, but none of us could have foreseen the challenges that the pandemic would bring. The rapid shift towards a remote work environment presented early challenges for biotech companies in particular, as so much of their operations are reliant on R&D in physical lab environments. This is one of the many headwinds that forced companies across the industry to swiftly adapt and evolve their operating models.

On the flip side, the current environment has created new opportunities for life sciences companies. We were already seeing increased investment of private and public capital into the sector, but this was intensified in 2020 as Covid-19 shone a spotlight on the industry and the solutions it can provide. It was a record year for investment in life sciences across almost every category and subsector – 3Q 2020 in particular was the largest quarter on record for venture investment in the sector. Alternative sources of capital also rose, including corporate VC and corporate partnerships, up-front payments and deal terms of partnership deals, and non-traditional investors, including individuals, angels, family offices, corporates, and hedge funds. Mega-rounds of funding continued to increase across biopharma and tools and diagnostics, as well as medical technology. Our overarching focus over the past year has been on delivering the capabilities, connectivity and network of J.P. Morgan to help our clients navigate this new landscape.

Do you believe that there is a renaissance in US manufacturing for life sciences on the horizon?

The impacts of Covid-19 have brought the realities of managing complex supply chains—including the potential risks and instabilities that it can present—to the forefront for life sciences companies. It created an opportunity for many businesses to re-evaluate the management of their supply chain, identify redundancies, and potentially introduce new processes or duplicate partners to create a more resilient supply chain. Across all industries, companies should be having the important conversation about how their supply chain will be managed based on a series of worst-case scenarios.

At the same time, we are seeing an emergence of personalized medicines, like gene and cell therapy.

Unlike biopharma's traditional wide-funneled supply chains that are built for volume, personalized medicines tend to have very specialized, complex, and narrow supply chains. This emerging demand is creating an opportunity for domestic manufacturing companies to enter the market or augment their business.

How has Covid and the shift to the virtual environment impacted how business is getting done in the life sciences space?

In some ways, Covid-19 and the digital-first environment have introduced new challenges and increased uncertainty. For example, if a potential investor is looking at a life sciences company's manufacturing facility, it could be difficult to arrange a walk through that would make them confident enough to invest.

At the same time, we've seen expanded capital options becoming available to companies that are looking to scale and drive growth. The injection of interest and investment into life sciences—from corporate partnerships to venture dollars—has opened up new avenues for growth for some of these companies.

The speed at which business can happen in a virtual environment is being recognized and it's something that will continue well beyond the pandemic.

Do you have any concerns regarding the influx of capital in the market?

I believe this influx of capital is overdue, and a net positive for the sector. It is important to remember that the life sciences industry remains a science and technology-driven space, and the value in these companies is built on the progression of science and the positive impact that it drives, rather than on more traditional metrics like customer traction or recurring revenue. The life sciences sector is also more easily quantifiable in the form of clinical data, and venture investors enter the space with the knowledge that science often takes time to progress and can be a longer-term investment. ■

James Gale

CEO
SIGNET HEALTHCARE PARTNERS

What themes has Signet honed its investment theses around for Fund IV?
We are now nearing the completion of the investment period in our Fund IV. The modalities that we invested in have had a tendency towards large molecule, as opposed to traditional smaller molecule. There has been more of an emphasis on newer technologies. The reason for the shift toward larger molecules, including cell and gene therapy, is due to the revolution presently taking place in medicine. Some of the gene therapy and cell therapy products have proven in clinical trials now to cure disease as opposed to just addressing the side effects. There is a paradigm shift taking place right now in the research resources being allocated. Those companies who are providing services to support that research are well positioned for substantial growth.

To what extent have you seen valuations shift over the past year, and do rising multiples impact the pace at which you deploy capital?
In the first half of 2020, valuations plummeted and a number of M&A transactions that were in process, ground to a halt. Buyers were concerned about business conditions and the longevity of the effects of Covid on the economy. Sometime into the third quarter, the M&A market and venture capital market regained confidence that the economy was returning to normal. Consequently, valuations rebounded and transactional activity sprung back to life. There have now been elevated valuations over the course of the last nine months, and it has made deal making a little bit more difficult for value buyers like us.

Do you believe investors will show interest in building more early-input capacity around APIs in recognition of the bottlenecks revealed by the pandemic?
Security of drug supply has now become a public policy question. There was a real risk in Spring 2020 that there could have been serious shortages of supply of life saving generic drugs. This near crisis has directed attention to the need to move the supply closer to home. That has been reiterated recently due to the recent export bans on supplies of Covid-19 vaccine from India and Europe. It is clear a disruption in any nation's supply chain can have enormous effects on the population. But, if the US is to create a domestic supply, will the market support it? Who is willing to pay the price associated with US production versus cheaper product from India? The current structure of the US generics market will have to be changed. Presently, there is little incentive for the distributors to support this national goal. I do not see economic players who are willing to finance repatriation of the drug supply chain to the US.

> **The reason for the shift toward larger molecules, including cell and gene therapy, is due to the revolution presently taking place in medicine.**

Do you agree with the notion that ensuring all drugs go generic without undue delay would be smart policy for the competitiveness of our healthcare system?
If the US wants to remain at the forefront of medical research and continue to develop these exciting new medications that are going to transform life in the next half century, we need to allow for adequate returns on those investments. There is a sanctity of this patent system that is essential. There has been considerable litigation and regulation over the past several decades which has created a framework around patent expiration. I am not sure how advisable it is to alter this system of rules that has been based on market interaction. That includes the ability of an innovator to extend the patent estate around their products. But, the legal test is whether these are true innovations or anti-competitive tactics. It is in that area that I think we need tougher standards to prevent a branded company from preventing generic entrants to the market.
I think the bigger issue concerns the way therapeutics are distributed. We should consider the allocation of the final consumer price to the various parties in the supply chain. There is enormous waste in the money being paid to distributors, retailers, PBMs and other intermediaries. A major solution to lowering US drug costs is in improving these intermediation costs. We should ask why parties who have not invested in innovation nor taken development risks, are taking a big portion of the price that the consumer pays. ■

Arda Ural

Americas Industry Markets Leader-Health Sciences and Wellness
ERNST & YOUNG LLP

What has been the overall impact of Covid on the life science industry?
With the exception of March and April 2020, life sciences companies generally came out unscathed by the immediate impact of Covid. However, demand was impacted as a large number of patients delayed elective medical procedures; this will likely have some carryover effect into 2021. The second impact was the delay of clinical trials, which we estimate will have an economic impact of US$34 billion over the next four years. This is because companies have struggled to get patients through the door to enroll them into non-Covid clinical trials. As a result, there will be some delays; although they have not yet impacted businesses from a value perspective, we foresee this as a potential headwind in the future.

2020 was a very strong year for biotech IPOs. What drove this trend?
Unlike 2008-2009, this is not a fiscal crisis; it is a pandemic, and there is a lot of liquidity in the overall system. In fact, biopharma alone, excluding private equity, possesses approximately US$1.5 trillion of liquidity to deploy. Because of this underlying strength, valuations, as evident by the S&P 500 Biotech or MedTech indexes, did not suffer at all. Consequently, IPOs and SPACs came back in a big way. Biotech IPOs are now at an all-time high and we do not foresee that stopping in the near term. ■

Christiana Bardon

Portfolio Manager
BURRAGE CAPITAL
Managing Director,
Oncology Impact Fund
MPM CAPITAL

Can you provide an assessment of the overall health of the biotech industry?
Biotech is riding a wave of positive sentiment these days. The reason behind that, is the incredible success we are seeing with Covid. The industry has quite literally saved the world by providing the vaccines, therapeutics and diagnostics we need to overcome one of the biggest crises the world has seen in the last 100 years. As a result, there has been a lot of investor interest in the sector. There has been a lot of enthusiasm for companies working on anything Covid related. However, in general, across the field of biotech there has been tremendous support for companies and their ability to raise capital. 2020 brought record financings for public and private biotech companies, and capital inflows have not just come from institutional funds, but retail as well.

Do the fundamentals driving biotech over the long term remain intact?
The three fundamentals that drive biotech are aging demographics, incredible innovation and the supportive regulatory environment. From that perspective, nothing has changed. The industry is creating many new drugs, which are going to go on to be approved and go out into a marketplace growing in medical need. The FDA's relationship with biotech has also been a very positive force for the industry and they have shown that if there is a severe unmet medical need, they can work productively and collaboratively to get drugs out to patients as quickly as possible. We saw the FDA perform at "warp speed" for Covid. But the truth is, they have been doing that same day job for years with respect to cancer and other severe unmet medical needs ■

Venture Capital

SCARCE TALENT MEETS ABUNDANT CAPITAL

Many people have an image of entrepreneurs as driven, dedicated, creative people who operate somewhat in isolation, maybe with a small group in a garage, maybe on their own, and who, come hell or high water, are intent on building the next big company, often with suffering and anguish along the way. It is viewed in many instances as an artisanal process, as if the entrepreneur is the business equivalent of the bohemian artist suffering for their craft.

The view of some of the most influential venture funds today is fundamentally different. Leaders in the industry, such as Flagship, Third Rock, Atlas and Arch, are pursuing a more systematic approach to the entrepreneurial process, that if applied with discipline and rigor, can lead to very surprising destinations. They all work by gathering a group of seasoned executives around an idea, often originating in university labs, then developed within their in-house incubators. The intellectual process is first about defining whitespace–areas of great unmet need, represented in therapeutics or advances in technology, or insights into science, where there has not been a dedicated or successful heretofore effort to figure out if there are ways of translating scientific ideas into value. If the hypothesis is deemed promising enough then a company is formed, financed and staffed by the VC.

In describing the evolution of Arch Venture Partners' model, co-founder & managing director Keith Crandell said: "In a way, we are still swinging with the chandeliers with the leading academics. That part has not changed from day one to today and we also follow the science, which they usually tell you in business school not to do. However, if you work with really powerful platforms, you can develop a level of confidence that there will be applications."

The nature of taking on these ambitious ideas is that these experiments often do not work, but when they do work they can work extremely well, grow very quickly and have an outsized impact. A portfolio approach is taken therefore with an understanding and appreciation of the asymmetric nature of the wins, relative to the odds that there will be some set of losses.

AVROBIO is a company incubated at Atlas Venture several years ago that has since exited into the public markets. Its creation was triggered by an opportunity to develop and scale potentially curative ex vivo lentiviral-based gene therapies to treat rare diseases. Reflecting on the opportunity being pursued, president and CEO Geoff MacKay observed: "While there have been just a handful of gene therapies approved in the US and Europe, I believe that we are entering a new era for this important modality. Hundreds of clinical trials around the world are advancing new investigational therapies for a wide array of indications. Not all will result in approved therapies, but many will. We hope to untether patients with serious genetic disorders from a lifetime of chronic treatments and deliver a functional cure with a single dose of a gene therapy."

Outsized Returns

The venture creation model has proven successful, producing strong returns for investors. Most venture capitalists look for returns that ultimately double or triple their initial investments, a 2x or 3x return multiple. In a report by stat news, it detailed returns of 9x on Flagship Pioneering's fund launched in 2012. As a result of this success and a coming of age of the biotech industry mixed with a raging bull market, fund sizes have reached astronomical levels. Flagship's latest fund, which closed in April 2020, raised US$1.1 billion, while Arch Venture Partners raised two funds totaling over US$3.3 billion in the past year.

Beyond those engaging in venture creation, the entire venture capital funding ecosystem for biotech not only hit an all time high, but it blew previous markers away. According to Pitchbook, over US$26 billion of venture funding went into US-based biotech firms in 2020. The prior high set in 2018 was US$19 billion. This is about 5x bigger than funding levels at the start of the biotech bull cycle in 2013.

These funds were raised on a much quicker timeline than historical norms — and pools of capital are much larger than ever before. All this makes for a particularly heady environment for startups in fields like cell and gene therapy that require a lot of expensive early work. Even for companies that are not as capital-intensive, more money usually means more options. If you have more money you can do more clinical trials and be generally more ambitious in pursuing moonshot programs. This much money floating around can also ratchet up the competitive tension between investors, as there is an excessive amount of money pursuing a finite number of assets and management teams.

Carolyn Ng, managing director of Vertex Ventures HC, who has stakes in portfolio companies such as Boundless Bio, Obsidian Therapeutics and Twenty-eight-Seven Therapeutics, remarked: "It is paradoxical that it is actually more challenging for fundamentals-focused funds like ours to make new investments in the current bull market. The reality is that our biotech VC industry is facing an unprecedented level of competition where there has been a massive influx of capital into the sector from traditional and new players going after a fairly limited pool of high-quality investment opportunities"

Ng continued, cautioning that while most financings occurring today are centered on great science, there is still a limit to which a company's pipeline can be derisked in terms of actual scientific and clinical risk, "We are witnessing a disconnect now between valuations and early-stage opportunities where scientific and clinical risks are still inherently very high," Ng affirmed.

When asked if the science supports the growing size of venture rounds we are seeing today, Arch's Keith Crandell offered: "I have gotten comfortable with it by observing the coupling of the capital with the quality and the track record of the managers that we are able to attract to help run these efforts. These are no longer single asset, single target projects that may have a finite amount of capital needed to take them through the project and then you are done. These are projects that are developing platforms, or in some cases multiple platforms with multiple compounds, often at multiple disease indications. To manage that and partner that effectively you need a very strong class of executive, and those executives basically have 360 degrees of opportunity with large biotech, large pharma, or smaller enterprises. If you do not have the resources to enable them to do the good work that they need to do, it is hard to recruit them."

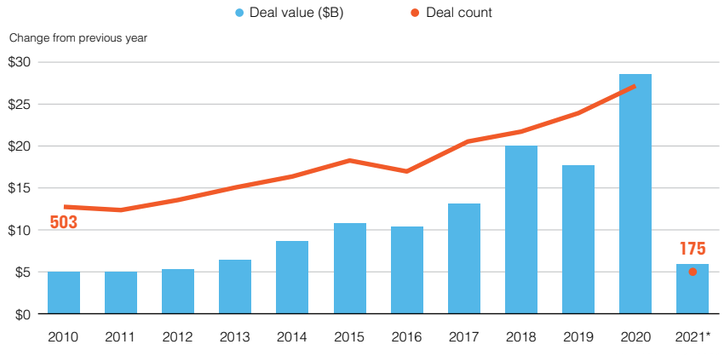
What happens when the merry-go-round slows?

More capital continues to flow into these funds creating one of the most auspicious environments for a start-up ever. The easy money with low interest rate theme along with outperforming IPOs has created a big feedback loop that incentivizes VC funds. However, as the cost of capital has dropped, the risks to the discipline of deploying it go up. As Atlas Ventures' Bruce Booth analagizes: "The average health of the herd goes down with an over-abundance of food sources."

Regardless of the environment, good management teams pursuing sound science will yield successful companies, but several factors, including a stricter regulatory environment around M&A deals, the adoption of price controls, higher interest rates, or failure on the part of payors to get on board with covering high-cost medications, could mean pain for companies that are mismanaged or pursuing some of the more speculative areas of science currently fueled more by hype than reality. "As long-term investors, we try to avoid herd mentality when it comes to chasing "hot deals", because to us, successful financing is a means to an end – the end being the delivery of outcome benefits to patients in the clinic," Ng concluded. ■

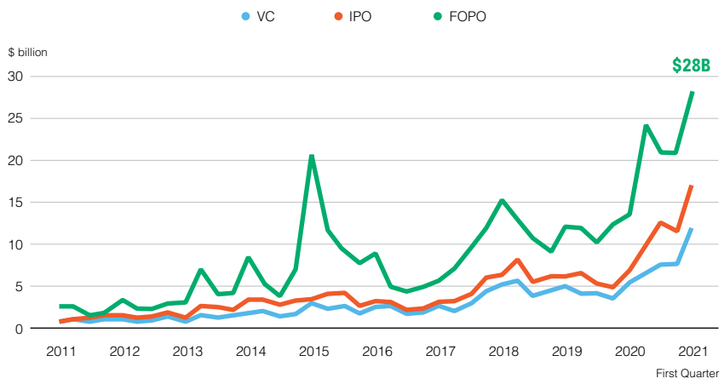
Biotech & Pharma VC Deal Activity

Source: PitchBook



Equity Capital Funding in Biotech

Source: VC data from Pitchbook; IPOs and FOPOs via Dealogic and ECM Analytics, courtesy of Cowen



We focus on the lead asset and how robust the data it generated is in determining if it passes through our diligence process. That data might come from a patient cell line or a rodent model or other preclinical translational models. Either way, our job is to distill down that data set, synthesizing all the data generated to date, and figure out if it is de-risked enough and if there is enough of a preclinical proof of concept where Xontogeny can build on that.

- Chris Garabedian, Chairman & CEO, Xontogeny

Keith Crandell

Co-founder & Managing Director
ARCH VENTURE PARTNERS

How has ARCH evolved its model over the years?
We follow the science, which they usually tell you in business school not to do - you are supposed to look to create a product to meet the market opportunity. However, if you work with really powerful platforms, you can develop a level of confidence that there will be applications. There are other things that we added that have improved the model. Some of that includes more access to capital, so that we can continue to be a strong supporter of our portfolio companies throughout their funding lifecycles all the way through IPO. We were very strong with our strategic limited partners in the early funds, and they were helpful in the portfolio companies as well. Now we have financial limited partners in our fund and have a special program that we set up called ARCH Technical Services to work closely with strategic groups that are like-minded about trying to work on innovative science and technology.

What are your thoughts on the growing size of venture rounds? Does the science support this trend?
I have gotten comfortable with it by observing the coupling of the capital with the quality and the track record of the managers that we are able to attract to help run these efforts. These are no longer single asset, single target projects that may have a finite amount of capital needed to take them through the project. These are projects that are developing platforms, or in some cases, multiple platforms with multiple compounds, often at multiple disease indications. To manage that effectively you need a very strong class of executive. If you do not have the resources to enable them to do the good work that they need to do, it is hard to recruit them.

What is the most scarce resource biotech companies must manage around today?
What is extremely valuable is insight and understanding where the industry is likely to evolve or where the puck is heading in the next three to five years. It is not good enough just to have the best science and then hope it all works out. Trying to thread together that combination of outstanding management, scientific innovation, scientific founders and then that clinical orientation in a way that allows them to work constructively and productively is the secret sauce. The timelines have been compressed; the rewards for being first in class, best in class and meeting unmet medical needs are pretty spectacular, but if you are the second person that makes it across the line the rewards are not terribly impressive anymore. Consequently, the key is to get it right the first time, which means you want to have all the pieces lined up in order to stand up as a global leader.

> **Trying to thread together that combination of outstanding management, scientific innovation, scientific founders and then that clinical orientation in a way that allows them to work constructively and productively is the secret sauce.**

What lessons can biotech take from the semiconductor industry about how to make things faster and cheaper?
I am a huge fan of the life science tools area and the impact it is having on diagnostics and ultimately devices. A lot of that comes down to having better measurements, more of them, with faster time to answer, and then lowering the cost per data point. A major part of the price drop in semiconductors is driven off the improvement in metrology, which is the measurement of all things inside the reactor, getting control of all those factors, and then allowing you to scale.
The entire innovation cycle works better and faster, and that plays directly to the smaller biotechs that are venture backed and in a hurry. They need better measurements, they need answers quicker, and they need high throughput, high capacity systems. These are all things that the semiconductor industry struggled with in the 70s and 80s and are now finding their way into the mix in biotechnology. Better data means more innovation, more discovery, intellectual property, opportunity, and it allows you to get there first. ■

Carolyn Ng & Lori Hu

CN

LH

CN: Managing Director
LH: Managing Director
VERTEX VENTURES HC

Can you describe the approach Vertex Ventures HC takes to portfolio construction and the platforms you currently find most appealing for investment?
CN: In terms of platform plays, there are novel chemistry platforms, novel biology platforms and other types of next-generation platform technologies for specific applications (e.g. regulation of cytokine expression). Within our portfolio, Bicycle Tx ($BCYC) is a great example of a novel chemistry platform, where Bicycle's scientific founder, Sir Greg Winter, who was awarded a Nobel Prize in Chemistry in 2018, invented bicyclic peptides, which in turn created a new universe of chemical matter with differentiated tumor-penetrating and PK properties. We have also made concentrated bets on breakthrough biological insights where we have a high level of conviction. These range from interrogating extra-chromosal DNA to target amplification oncogenes with Boundless Bio (founded by UCSD's Paul Mischel), to critical biological insights into glycan-mediated immune regulation in oncology and inflammatory diseases with Palleon Pharma (founded by Stanford's Carolyn Bertozzi), to first-in-class approaches of targeting RNA-binding proteins, which underpinned our investment thesis in 28-7 Tx (founded by Harvard's Dean George Daley and co.). In addition, there are unique cytokine regulation platforms like Obsidian, where they are developing IL-15-regulated engineered TILs (Tumor Reactive Lymphocytes) cell therapy that could potentially obviate the need for IL2 treatment.
There are also ways of conceiving platform concepts with unique business models. This perspective led to our investment in Elevate Bio's Series B last year. They have a central cell and gene manufacturing facility called Basecamp on one hand, and about half a dozen cell and gene therapy programs incubated and founded with different scientific founders on the other. Not only does the central facility Basecamp serve process development and manufacturing needs of its in-house incubatee companies, it also provides such services to non-Elevate companies. The structure is analogous to Bridge Bio's model and we are excited to see this model gaining significant investor traction when they raised the US$525 million Series C recently.

How has the influx of capital affected the biotech investment landscape?
CN: It is paradoxical that it is actually more challenging for fundamentals-focused funds like ours to make new investments in the current bull market. The reality is that our biotech VC industry is facing an unprecedented level of competition where there has been a massive influx of capital into the sector from traditional and new players, going after a fairly limited pool of high-quality investment opportunities. Most of these financings are centered on great science, but one has to recognize that there is still a limit to which their pipeline could be derisked in terms of actual scientific and clinical risk. In short, we are witnessing a disconnect now between valuations and early-stage opportunities where scientific and clinical risks are still inherently very high. As long-term investors, our we try to avoid herd mentality when it comes to chasing "hot deals", because to us, successful financing is a means to an end – the end being the delivery of outcome benefits to patients in the clinic.

Where does regulatory oversight rank in your criteria when evaluating an investment?
CN: Our portfolio is heavily weighted in areas such as oncology and orphan diseases, where regulatory aspects of drug development have largely been favorable. Generally speaking, we have seen FDA being open to collaborate and willing to provide feedback to early-stage biotech companies on the development path of a clinical program. Regulatory challenges are of course different outside of oncology or rare indications, or for cases where clinical evidence is ambiguous at best. We are seeing this now with the case of Biogen's aducanumab for Alzheimer's Disease, which has been contentious.

What areas of biotech do you believe have potential transform the industry over the next decade?
LH: We have seen a lot of traction in the gene editing space and we still like the fundamental science. CNS is an area we invested in as well, which is higher risk biology, but we believe there is huge unmet need and great opportunities. We have not done as much with pure play AI and machine learning drug discovery platforms, which could be a very promising for the field. However, we are still awaiting more proof of concept in terms of the drugs that come out of the platforms and how they perform in the clinic relative to more traditional drug discovery. ■

Chris Garabedian

Chairman & CEO
XONTOGENY

How can friction in the early-stage ecosystem be lessened so that the right deals happen more easily?
Historically, you had about a dozen very well-known VCs who were almost exclusively doing series A company creation. When these VCs close a fund, they are not starting 50 companies. Even if they have a billion dollar fund, they are trying to put US$100 million into 10 companies. Therefore, while we have seen an infusion of new capital come into the space, it has not necessarily resulted in the same proportion of new companies. This means that entrepreneurs have not had many funding options if they do not "win the lottery" by being picked by one of those VCs. In fact, the cards might even be stacked against them, because they are not going to want to take a US$100 million series A round, if it means dilution for them. For that reason, many of them have eschewed the company creation model. That is why I started Xontogeny to have a founder friendly, supportive option. We wanted to provide a home for that true entrepreneur, scientific founder, or first-time CEO. There are a plethora of cool technologies out there, and the funding of these companies should not be dominated solely by billion-dollar VC funds.

What do you see as the principal advantage of accelerators, and what is Xontogeny able to offer that others are not?
It is important to distinguish between incubators and accelerators. Most biotech incubators are doing drug discovery research, and often they have a thesis that they have not yet proven, or they have not filed intellectual property. However, they are hoping that if they work on incubating a new idea or new technology this will lead to a patent that they can file. That is the starting point of the potential to create a company that gets funding.
For the most part, the bulk of researchers or companies that populate incubators are very early stage. They often have not achieved preclinical proof-of-concept, and many of them will struggle to raise enough capital to take things very far. You see some incubators that are attached to university systems, but they are separate, because you have companies or researchers that do not want to be encumbered by research done at the university. We see the advent of the large lab space business model, which may be called incubators, and some examples include J&J's J-Labs, Alexandria's LaunchLabs and LabCentral's BioLabs, to name a few.
Accelerators differ from incubators in that they are taking those technologies and surrounding early research with the right support. That might be virtual support, it might be active management support, but accelerators are taking those promising technologies and turning them into viable development programs and potentially investable companies. At Xontogeny, we often are the first seed or founding capital into these companies that might have previously subsisted on grant money or their own personal investment. We describe ourselves more broadly as an accelerator, because we are taking companies and trying to accelerate them into development and allow them to get the chance to be invested in with a healthy, series A. That is where the Perceptive Xontogeny Venture Fund comes in. The valley of death is where companies often get stuck between US$500,000 to US$3 million seed capital. Usually, it is because a company does not have a compelling enough story, or it is not de-risked enough with pre-clinical proof-of-concept data to invite a venture firm. What is needed to bridge that valley of death usually requires at least US$10 million to get into the clinic and/or through an initial clinical study.

What makes a compelling investment target for Xontogeny?
Xontogeny is very focused on the lead asset that is closest to clinical development. Specifically, we are focused on advancing the lead candidate through preclinical stage, de-risking to get through some good translational work, adopting the right regulatory strategy, getting as quickly as we can into dose safety studies and possibly through a clinical proof-of-concept study with a healthy Series A financing. ■

> We wanted to provide a home for that true entrepreneur, scientific founder, or first-time CEO.

Hub and Spoke

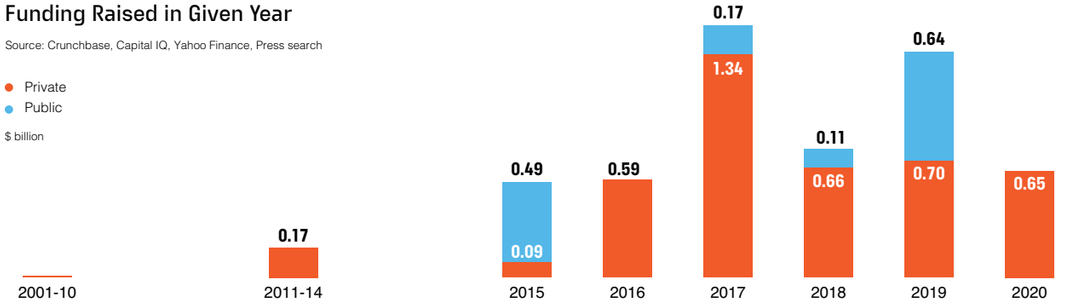
A NEW MODEL TO CURE DISEASE

MIT's Andrew Lo, one of the leading advocates of the portfolio approach, gives a lecture that goes like this: The 'omics' revolution is a marker of tremendous progress in the life sciences. There is genomics – the study of the sequence of the human genome, epigenomics – the study of the on/off switches that cause certain genes to be expressed and others to be suppressed, transcriptomics – the study of how these gene sequences get translated into proteins, proteomics – the study of the 20 to 25,000 different proteins that make up the human body, metabolomics – the study of all the chemical reactions that occur to make life possible, and, most recently, microbiomics – the study of the bacterial colonies that inhabit the body and provide us with all sorts of important functions. All of these 'omics' have experienced tremendous advances over the last few years, with the exception of one, and that exception is econ-omics. The fact that we still need to figure out better ways of paying for all of these therapeutics is where the bottleneck occurs.
A successful new drug might pay off US$2 billion per year for a decade and only cost US$200 million to create. However, the chance of success is low (5%); even with that payoff, many investors balk at the risk.
The essential question is: what if you could pool the risk? Lo proposed creating a US$30 billion fund to finance 150 biotech startups (US$200 million each). The key insight was that each startup had to target a different (and unrelated)

> *Deciding to focus on Phase 2 and Phase 1 assets requires us to assume risk and be patient. There are two critical factors that matter as we think about a monetization transaction: 1) Is there a pharmaceutical partner or well-funded biotech doing the clinical development work? 2) How predictive is early data of a positive ultimate outcome? Not all therapeutic areas are created equal in that respect.*
>
> **- James R. Neal, CEO, XOMA**

Funding Raised in Given Year

Source: Crunchbase, Capital IQ, Yahoo Finance, Press search



2001-10
Founded

PureTech Health

Biohaven

BridgeBio

2011-14
Notable funding raised

Roivant (PE)

PureTech (growth stage)

Nimbus (Series A)

2015
Founded

Gossamer Bio

Notable funding raised

PureTech Health (IPO)

2016
Notable funding raised

Roivant (PE)

Biohaven (venture)

2017
Notable funding raised

Biohaven (IPO)

Roivant (PE, $1.1B from Softbank)

2018
Notable funding raised

Gossamer (Series A and B)

Roivant (PE, $1.1B from Softbank)

2019
Founded

ElevateBio

Notable funding raised

Gossamer Bio (IPO)

BridgeBio (IPO)

2020
Notable funding raised

BridgeBio (post-IPO debt)

ElevateBio (Series B)

disease. Lo wanted all of the startup bets to be completely uncorrelated, meaning failure by one would have zero effect or relation with another. Using this model, his research showed that the odds of finding one successful drug would be greater than 99%. The odds of finding five drugs would be over 87%. This approach effectively de-risked biotech funding for the most conservative and largest investors in the world.

With this knowledge, Neil Kumar, one of Lo's students, went on to found Bridge Bio, which alongside Roivant Sciences and PureTech Health, are pioneering the execution of the portfolio model. Others like Elevate Bio have followed with a US$525 million series C and Centessa with their US$250 million series A, founded by Moncef Slaoui, who ran operation warp speed during the Trump administration.

Vertex Ventures HC managing director Carolyn Ng has taken notice of the promise in the space. "There are ways of conceiving platform concepts with unique business models. This perspective led to our investment in Elevate Bio's Series B last year. They have a central cell and gene manufacturing facility called Basecamp on one hand, and about half a dozen cell and gene therapy programs incubated and founded with different scientific founders on the other. Not only does the central facility Basecamp serve process development and manufacturing needs of its in-house incubatee companies, it also provides such services to non-Elevate companies," NG commented.

One of the key reasons this model is gaining so much traction is due to the success of the early movers in the space. PureTech Health, for example, has 22 therapeutics and therapeutic candidates of which 15 are clinical stage and 2 have been granted FDA clearance and European marketing authorization. In conversation with PureTech's founder and CEO, Daphne Zohar, she explained that the group decided that, given the fund's initial scarcity of resources, it would fund new medicines that it developed by putting them into subsidiaries (Founded Entities). This allowed the company to share the cost of development with investors to advance those medicines. As those programs progressed and PureTech developed a track record of multiple clinical successes, that generated more resources and consequently, they have been able to keep ownership of new programs and develop those internally. These make up their wholly owned pipeline.

Bharatt Chowira, who joined PureTech as president and chief of business and strategy after a stint running Synlogic, highlighted the fact that because of PureTech's model, its Founded Entities are very well funded and have excellent independent management teams. "We see them as partnered programs that are generating value for us but do not require a great amount of our resources at this point. For example, we brought in about US$347 million from the sale of equity in Karuna in 2020. We are still a major shareholder in Karuna and we still have equity and royalties, but that gave us flexibility that many biotech companies do not have," said Chowira.

In the case of Roivant Sciences, they are organized as a decentralized family of biotech business units that they call Vants. Their view is that innovation in biopharma most often occurs through small teams with skin in the game. Their model is designed to recruit top talent and incentivize management teams based off of the individual projects they are working on. Under the leadership of Matthew Gline, who replaced Vivek Ramaswamy as CEO this year, the company will

continue its Vant portfolio approach. However, the intent is also to build out its capacity in computational drug discovery and tech-enabled clinical trial monitoring. In their view, they are building one of the first large scale pharma-tech companies.

In Matt Gline's words: "Historically, when our team came up with an idea, such as targeting the neonatal Fc receptor, we would boil the ocean and find drugs at academic centers, biotech companies, and big pharma that matched our hypothesis. We then would in-license, acquire or partner on those therapies. That is still a big part of who we are as a business, however, we started to realize that our engine for finding promising targets would sometimes produce a target that we could not acquire. For the most part, up until recently, what we did with those targets was to put them in the discard bin. The discard bin eventually became full, and at the same time some of the data scientists working on target identification made the case that we could do better at using machine learning to design new medicines."

With that insight, Roivant formed a unit called VantAI to discover and develop more medicines in house, and notably acquired Silicon Therapeutics in February. The company has what Roivant believes is the most precise computational molecular dynamics toolkit in existence. "Now we can take a new and difficult problem like degrading a tough to hit protein like p300-CBP, and we can simulate that system's atom-by-atom design using Silicon Therapeutics' toolkit. Consequently, we get this unique flywheel that comes from the combination of molecular dynamics, medicinal chemistry, wetlab and machine learning, which is a rarity for a company to have all under one roof," Gline affirmed.

Royalty Monetization

Another form of portfolio construction gaining attention over the past year is the royalty monetization model. There have long been well-established royalty businesses, yet most have been privately held. 2020 marked a resurgence of interest in royalty aggregators as an investment vehicle when Royalty Pharma's IPO was valued around US$30 billion, one of the largest of the year. XOMA is another of the pure-play royalty aggregators in the biotech space. Their CEO James Neal explained: "We help biotech companies fund their businesses by employing our milestone and royalty monetization model, which is unique from other royalty aggregators in this space. In simple terms, royalty monetization is the exchange of the potential future at-risk economics for cash today."

This can be an extremely important form of financing because companies who license their invention to another typically put that up-front capital to use by funding innovation and clinical trials. Neal elaborated: "The originator, the company who is entitled to receive economics on the out-licensed asset, may decide it is in their best interest to sell the potential future license agreement economics in exchange for cash today, versus waiting for what could be five-plus years to see meaningful financial returns." ■

James R. Neal

CEO
XOMA

What are the key advantages of the biotech royalty aggregator model?

We help biotech companies fund their businesses by employing our milestone and royalty monetization model, which is unique from other royalty aggregators in this space. In simple terms, royalty monetization is the exchange of the potential future at-risk economics for cash today.

Companies who license their invention to another typically put that up-front capital to use by funding innovation, clinical trials, etc. The originator, the company who is entitled to receive economics on the out-licensed asset, may decide it is in their best interest to sell the potential future license agreement economics in exchange for cash today, versus waiting for what could be five-plus years to see meaningful financial returns.

That's where XOMA comes into play – we acquire the future economics to assets that are still in Phase 2 and Phase 1 development. Our approach to royalty aggregation provides capital for the biotech community to be able to advance additional innovative candidates.

Are there certain characteristics that make an asset more appealing to XOMA?

Deciding to focus on Phase 2 and Phase 1 assets requires us to assume risk and be patient. There are two critical factors that matter as we think about a monetization transaction: 1) Is there a pharmaceutical partner or well-funded biotech doing the clinical development work? 2) How predictive is early data of a positive ultimate outcome? Not all therapeutic areas are created equal in that respect.

How does XOMA view big pharma as potential partners?

Pharma companies have the expertize, capital, talent and global reach to fully explore the potential of an asset at Phase 2 and pick the indications that have the best chance of succeeding in Phase 3. They have the infrastructure in place to get the therapy to physicians and patients. They are able to negotiate pricing and reimbursement on a country-by-country basis. ■

Daphne Zohar & Bharatt Chowrira

DZ: Founder and CEO
BC: President and Chief of Business and Strategy
PURETECH HEALTH


DZ


BC

> We think that as we move forward and drive our internal pipeline through advanced clinical development and commercialization, we are building a major biopharmaceutical company.

What is the genesis of PureTech Health and what inspired you to start this company?
DZ: As an entrepreneur, I was interested in how academic breakthroughs get translated from basic science to the point where they impact patients. There was an existing ecosystem in place and usually it entailed an entrepreneur or scientist advancing one specific idea. The most compelling entrepreneurs and scientists get funding and there is attrition along the way. What occurred to me was that at the beginning of the process, those individuals were advancing their own ideas but not necessarily looking broadly and asking what the best idea is. The approach at PureTech was that we were going to look at a landscape of the most exciting scientific breakthroughs together with leading experts and do that through the lens of a specific disease. That process forces you to look at a number of different approaches one can take in a modality agnostic way.
We decided that we would fund the new medicines that we develop by putting them into subsidiaries (Founded Entities). That way we could share the cost of development with investors to advance those medicines. As those programs progressed and we developed a track record of multiple clinical successes, that generated more resources and we were able to keep the ownership of new programs and develop those internally.
BC: Because of the model that we had, those Founded Entities are very well funded and have excellent independent management teams. We see them as partnered programs that are generating value for us but don't require a great amount of our resources at this point. We do not have to go out and always tap the capital markets for funding.

PureTech's programs have breakthrough potential but are also risky. How do you help mitigate these risks?
BC: Across both our Wholly Owned Pipeline, and our Founded Entities we have diversification of risk because our pipeline does not rely on one platform or program and our value is underpinned by a significant group of de-risked assets to counter some of the more risky, earlier stage programs.

If you are a biotech entrepreneur what are some of the issues in the earliest phases?
DZ: There is a tension between elements that don't exist when one is starting a business, such as funding, people, and a great technology. All of those elements are drawn to each other, so if you do not have money it is really hard to attract great people. If you do not have great people it is hard to attract money, and if you do not have either of those it is hard to get the technology in place and licenses. The job of an entrepreneur is to overcome that inertia and find a way to bring in those pieces when they do not exist. Biopharma is an industry that is somewhat risk averse and pattern recognition oriented, so whenever you have a different business model, you often need to prove that it works before you get a lot of credit for it.

What goals do you wish to achieve over the next 2-3 years and how might this strategy reward shareholders taking a long-term view of PureTech?
DZ: We will not look like Merck or Pfizer, because we are set up in a more entrepreneurial way. However, we think that as we move forward and drive our internal pipeline through advanced clinical development and commercialization, we are building a major biopharmaceutical company. Shareholders that are joining us today have the opportunity to benefit from our fulfilling that mission. It has to do with making a difference in the lives of millions of patients, and we are proud of the fact that PureTech has 24 product candidates that we invented or initiated. 13 of these are in clinical testing, and two have received FDA clearance. We feel that our model also protects downside for investors, because we have multiple modalities along with our Founded Entities that are a source of value for us. ■

Matthew Gline

CEO
ROIVANT SCIENCES

> We are building one of the first large-scale pharma-tech companies. We use technology in every aspect of our business, from computational drug discovery to tech-enabled clinical trial monitoring.

Why is Roivant's business model considered to be pioneering in its approach?
First, we are building a next-generation big pharma company structured as a family of companies. Unlike today's large pharma companies, Roivant is not a single monolithic command-and-control organization. Instead, we are organized as a decentralized family of biotech business units that we call Vants. Our view is that innovation in biopharma most often occurs through small teams. By virtue of our distinctive corporate structure, we are able to recruit top talent and incentivize management teams based off of the individual projects they are actually working on. The second point of differentiation is that we are building one of the first large-scale pharma-tech companies. We use technology in every aspect of our business, from computational drug discovery to tech-enabled clinical trial monitoring. Our embrace of technology is not an end in itself, but rather a means of accomplishing our ultimate goal, which is to develop as many medicines we can for patients as fast as we can.

How has Roivant's model of in-licensing drugs with early-stage clinical data now shifted to building and designing molecules from scratch?
It has always been the core of who we are to identify biological targets and pathways of interest. We have always done this through interdisciplinary teams that combine data scientists with MD-PhD investor types and translational and development scientists. Historically, when that group of people came up with an idea, such as targeting the neonatal Fc receptor, we would boil the ocean and find drugs at academic centers, biotech companies, and big pharma that matched our hypothesis. We then would in-license, acquire or partner on those therapies. That is still a big part of who we are as a business, however we started to realize that our engine for finding promising targets would sometimes produce a target that we could not acquire. For the most part, up until recently, what we did with those targets was to put them in the discard bin. The discard bin eventually became full, and at the same time some of the data scientists working on target identification made the case that we could do better at using machine learning to design new medicines.
Some of these targets are well situated for the use of machine learning in drug design so we formed a unit called VantAI focused on that problem. We became increasingly interested in this avenue as an additional source of growth, and we have built some really unique capabilities both in terms of computational chemistry and in terms of wetlab medicinal chemistry to make that a reality. That becomes yet another important new source for medicines, so that when we cannot find something to in-license, we can attempt to discover and develop it in house.

What impact do you see computational drug discovery having on the industry, and how will Roivant's acquisition of Silicon Tx boost the company's positioning in the space?
Our view is that this is going to be an incredibly impactful set of technologies that could change all aspects of drug discovery. We have chosen to focus specifically on the design of novel small molecules. We are particularly optimistic about targeted protein degraders as a future modality. These are bifunctional small molecules that have a number of interesting properties. For example, you do not need to bind to the active site of a protein in order to degrade it. This is an area of medicine ripe for computational applications. We realized that the machine learning toolkit that we already built in Vant AI is incredibly powerful when you have a lot of data about a system or related systems in order to make predictions. However, sometimes the problem you are trying to solve has no good data out there. In that situation, you want to be able to go back to first principles.
Designing a new computational molecular dynamic simulation from scratch is hard, but we got really lucky in the relationship we built with Silicon Therapeutics. They have what we think is the most precise computational molecular dynamics toolkit out there. Now we can take a new and difficult problem like degrading a tough to hit protein like p300-CBP, and we can simulate that system's atom-by-atom design using Silicon Therapeutics' toolkit. ■

ACCELERATING PIPELINES

"Hundreds of clinical trials around the world are advancing new investigational therapies for a wide array of indications. Not all will result in approved therapies, but many will."

- Geoff MacKay,
President and CEO,
AVROBIO

Image courtesy of Insmed

Expanding Therapeutic Focus

IMPROVING QUALITY OF LIFE

In addition to heavily studied areas like neurology and oncology, the scope of companies developing therapeutics that target unmet medical needs has widened dramatically in recent years. Indications that have been without effective treatments for decades are now gaining renewed attention, while others with a well-entrenched standard of care have companies seeking to redefine treatment paradigms, in some cases even offering cures. This is happening across single-gene disorders, such as cystic fibrosis or Huntington's disease, as well as common polygenic diseases, such as diabetes and heart disease. Researchers are making remarkable progress in targeting the underlying genetic basis of disease rather than symptomatic relief. The resulting therapeutic gains are awe-inspiring, and a slew of drugs are being developed to benefit patients.

One of the most obvious areas of need is in the autoimmune disease space. Psoriasis and ulcerative colitis are just a few diseases in this area with large addressable markets. For context, AbbVie's Humira brought in US$19.83 billion in revenue in 2020. Furthermore, it is anticipated that this market will continue to grow as countries become more industrialized. This has led to a "hygiene hypothesis" which suggests that, as we evolve into a cleaner society that is less exposed to things humans were exposed to historically, we are not challenging the immune system as much anymore, ultimately leading to more autoimmune disease.

The autoimmune indication market is expected to be worth US$153 billion by 2025, and companies like Blacksburg-based Landos Biopharma could be poised to benefit immensely. Landos CEO, Josep Bassaganya-Riera, underlined that the company's initial autoimmune indication focus was on Crohn's disease and ulcerative colitis (UC), two diseases with an extremely large unmet medical need and a multi-million dollar market. "The way we are approaching autoimmune diseases is by focusing on targets at the intersection of immunity and metabolism. We are leveraging our AI-based integrated computational platform to identify important new molecular targets," he said.

Another player with a drug addressing UC is Arena Pharmaceuticals, which this February completed full enrollment of its Phase 3 ELEVATE UC 52 trial evaluating the safety and efficacy of Etrasimod. "There are 150,000 moderate ulcerative colitis patients in the US that have ongoing active disease and are currently treated by older agents like 5-ASA and pulse steroids. These are prime candidates for receiving a once a day oral that has the profile of Etrasimod," Amit Munshi, president and CEO of Arena, commented.

> *Covid-19 has exposed that baseline health is critical to manifestations of the virus. From an investor standpoint, metabolic diseases represent a high bar due to there being such a complex polygenic and environmental interaction, and cardio-metabolic diseases have been deemphasized in the investment community. Covid-19 has brought back the importance of obesity as it puts one at high risk. I hope that in the near future there will be renewed interest from investors in chronic disease because of its interplay with acute viral infections.*
>
> **- Joyce Harper, CEO, Ferox Therapeutics**

let it resolve on its own for 13 months. However, Novan seeks to solve this in 12 weeks.

In explaining the company's technology, Paula Brown Stafford, president and CEO said: "Nitric oxide is a heavily researched molecule, but there have been challenges associated with controlling the release of the gas and the ability to stabilize and store it. That is what Novan has been able to do with our NO Platform. We store nitric oxide on a polysiloxane backbone, using our proprietary Nitricil technology, and then we can tune the timing and duration of the NO release via our formulation science."

Ophthalmology

Another area of huge unmet need is in the field of ophthalmology. As it stands now, for the many diseases affecting the back of the retina, treatments are either non-existent, or there is a significant population of non-responders to available therapies representing a large, underserved population. For example, dry age-related macular degeneration, which leads to irreversible blindness due to degeneration of the retina, has no available treatment and an estimated US patient population of nine to 10 million. For other retinal diseases, such Retinis Pigmentosa or Leber Congenital Amaurosis, there are no available treatments.

This is why Ocugen, in addition to spending the past year developing a Whole-Virion Inactivated Vaccine for Covid-19 alongside Bharat Biotech (COVAXIN), has a program developed through its modifier gene therapy platform that targets nuclear hormone genes (NHRs), which regulate multiple functions within the retina.

According to Ocugen's CEO and co-founder Shankar Musunuri: "By targeting a functioning nuclear gene like a NR2E3, it upregulates all the functional networks associated gene expressions, resets homeostasis, and restores normal cell function."

that are sitting in a freezer, which we then expand by fermentation to create a product that is always going to have the exact same composition, potency and dose."

Vedanta's platform also allows it to address scalability issues common in the field, because they produce the drug by fermentation, enabling them to scale up production to make as needed at a much lower cost of goods than a donor-derived procedure. Olle's ambitious agenda is fueled by a belief that microbiome therapeutics will see major breakthroughs that will fundamentally change the biotech industry in the coming years. "Our ultimate vision is to enable defined consortia of bacteria as a new drug modality, in the same way that Genentech enabled protein biologics and Alnylam enabled RNAitherapies as new modalities," he proclaimed.

In the realm of dermatology, Novan, whose proprietary nitric oxide technology came out of the University of North Carolina Chapel Hill in 2008, is also leveraging its platform with anti-microbial and anti-inflammatory properties to address skin diseases with unmet needs. Its SB206 seeks to treat Molluscum patients. It is a highly contagious disease that can spread to become as many as 100 lesions on the body. The current standard of care is to

On account of this, Ocugen has received four orphan designations from FDA and orphan medicinal product designation for the treatment of both Retinitis Pigmentosa and Leber Congenital Amaurosis from the European Commission.

Rare and Orphan Disease

Until the Orphan Drug Act was authorized in 1983, many rare diseases remained unaddressed – in truth, orphaned by the industry due to complex biology, challenges with diagnosis, difficult patient identification, and other issues including navigating market access hurdles across multiple geographies. Thankfully, today things have progressed substantially. Specifically, in 2020, the FDA approved 32 novel drugs and biologics with orphan drug designation. "There has been an immense amount of advance as a result of the Orphan Drug Act… This act prompted industry to turn its attention toward these diseases, and NTM is one such disease which fits that description. It is common in that pathogens are ubiquitous in the environment, so we are all exposed to it, but only a very small group of people develop it into an indolent disease that requires treatment. It numbers around 100,000 patients in the US, of which we went after the most severe, the refractory population, which numbers between 12,000 and 17,000," commented Insmed CEO, William H. Lewis, who is leading the charge to bring ARIKAYCE, the first ever approved therapy for the treatment of NTM to market. Lewis added: "The results have been gratifying because we saw almost a third of the patients with no evidence of infection after treatment with our drug in our phase three trial."

Another important approval that came in 2020 in the orphan disease space is LFB USA's Sevenfact. This product is indicated for Hemophilia A and B patients with inhibitors. It represents a relatively small market the company is treating. "Even though there is a substantial Hemophilia patient pool, once you go into the A&B patients with inhibitors, there are less than 1,000 patients in the US. It is a targeted market, with only one other product approved, and that product has held a monopoly position for many years. As a result, LFB had a very big incentive and was determined to bring an additional choice to these patients," opined Jose Antonio Moreno Toscano, CEO of LFB USA.

Development of a pharmaceutical product and getting FDA approval are important first steps. However, regulatory approval does not always equal commercial success. Commercial success, especially with products under orphan drug designation, is challenging. Your work with payors needs to be very targeted and clear.

- Jose Antonio Moreno Toscano, CEO, LFB USA

Because patient pools in Rare and Orphan disease are small, patient advocacy groups can play an essential role in driving innovation, fundraising and clinical trial development. For this reason, companies must cultivate close relationships with the patients they are attempting to serve. "You cannot run your communications for investors sake only. There are many companies that still try to do that; they become public, and they realize that they have obligations to their shareholders and that drives the communication. That way won't scale long term. What you really need to do is build a foundation of key messaging and positioning aligned with key audience if you are in rare disease patient communities. All of that communication and relationship building builds up to creating value for the company," explained Donna LaVoie, a strategic communications expert who leads LaVoieHealthScience.

Cystic Fibrosis

Many CF patients experience symptoms involving the digestive system, which are often associated with the production of a thick mucus in the pancreas that blocks the release of the digestive enzymes needed to break down food. This deficiency in exocrine pancreatic enzymes, resulting in a patient's inability to digest food properly, is referred to as EPI. To treat EPI, CF patients often need pancreatic enzyme replacement therapy (PERT), a treatment designed to supplement enzyme levels to the digestive system. Enzymes used in PERT are typically derived from pigs or other animals, prompting the development of alternative formulations not derived from animals. The active ingredient in AzurRx's MS1819 is a synthetic enzyme derived from yeast cells, thereby avoiding the use of animal products. James Sapirstein, president and CEO of AzurRx BioPharma, reflected: "When I first started my career with Eli Lilly, we had a product derived from the recombinant DNA of E. coli called Humulin. The intent was to replace 85 years of porcine-derived insulin in diabetic patients. It took Lilly a few years, but human insulin eventually became the standard of care. We see our MS1819 yeast-derived recombinant lipase as analogous."

The benefits of the AzurRx approach are that it does not have the same antigenicity issue as a porcine-derived product. The production process will also be safer, standardized and more consistent. "We are not depending on pig herds that sometimes get slaughtered because of swine flu or for some other reason. More importantly, MS1819 requires the ingestion of fewer capsules each day. As a pharmacist, compliance is key. The less medication required, the more compliant the patient will be," Sapirstein expounded.

Progressing Behind the Scenes

It is important to recognize that while the dominant headlines of 2020 were about progress made across the industry with respect to Covid vaccine development, there was also much progress made in areas that for a long time have been completely neglected. It is a strength of the US healthcare system that there are private companies who willingly embrace enormous financial risk to bring drugs to market for small and large segments of the population. This has hugely beneficial implications for patients, and gives renewed hope to those who once thought they would never be cured. ■

James Sapirstein

President & CEO
AZURRX BIOPHARMA

What are the biggest differences between the AzurRx of 2020 and that of 2021?

AzurRx has gone through a major transformation over the past year. This was driven by our ability to raise a substantial amount of capital in 2020 and into 2021. We also brought in a new clinical-stage asset through an exclusive worldwide license agreement with First Wave Bio. The asset is a micronized version of niclosamide that we are developing as a treatment for two indications - Checkpoint Inhibitor Colitis and Covid-19 GI infections. We expect to initiate clinical trials for both indications in the first half of 2021. In addition, AzurRx continues to advance its clinical program for our lead investigative candidate, MS1819 in cystic fibrosis. We expect to report topline data from the OPTION 2 monotherapy study at the end of Q1. Finally, the combination therapy trial for MS1819 continues and we fully expect to hit our topline data timeline of Q2 2021.

What is the potential for MS1819 to replace PERT as the standard of care for exocrine pancreatic insufficiency (EPI)?

When I first started my career with Eli Lilly, we had a product derived from the recombinant DNA of E. coli called Humulin. The intent was to replace 85 years of porcine-derived insulin in diabetic patients. It took Lilly a few years, but human insulin eventually became the standard of care. We see our MS1819 yeast-derived recombinant lipase as analogous. Why? Because MS1819 is more humanized, it does not have the same antigenicity issue as a porcine-derived product. The production process will be safer, standardized and more consistent. We are not depending on pig herds that sometimes get slaughtered because of swine flu or for some other reason. More importantly, MS1819 requires the ingestion of fewer capsules each day. The reason patients need to take so many capsules with PERT is that they are taking a product made of crushed pig pancreas and you are not really sure how much enzyme they are receiving so you must overcompensate by administering a large number of capsules.

What made the AzurRx-First Wave Bio in-licensing agreement an appealing deal?

Our primary interest in niclosamide was as a treatment for Immune Checkpoint Inhibitor Colitis. But data from the Institute of Pasteur in Korea indicated that in Covid-19, niclosamide had the best activity in terms of eradicating the virus. The other appealing aspect was Gary Glick, the founder of First Wave Bio. Gary is a gifted chemist and has been prolific in the oncology space. He has had major exits with Novartis, BMS and Merck, so when Gary approached me about looking at niclosamide, we were immediately interested.

What is exciting about niclosamide is the unmet need. Studies demonstrate that 48% of all Covid-19 patients have positive virus RNA in their stool samples. Therefore, this means that almost one-half of Covid patients still have viral RNA in their GI tracts, despite being considered 'cured' of the disease. We also know that approximately 20% of all Covid-19 patients have disease-related GI infections, so whether you are vaccinated or not, you are still at risk for getting Covid in the future. We believe niclosamide could be a first-line therapy for this virus. As with HIV, we are going to have to drug our way out of this pandemic. The available vaccines and those in development are tremendously beneficial, but certainly not a cure-all. We are betting that the gastrointestinal tract is where the virus hides, and niclosamide could eradicate Covid-19 from the GI tract.

What does the improved financial position of AzurRx mean for the progression of MS1819?

One issue facing MS1819 has been manufacturing. Before my arrival, AzurRx did not spend a great deal of capital on manufacturing, but rather the company was financing to the next clinical endpoint. We are investing capital to augment our manufacturing. The Phase 2b trials are underway and we anticipate having an end of Phase 2 meeting with the FDA towards the end of 2021. At that point, we hope to be able bring in a strategic partner to get us through Phase 3. ■

We are betting that the gastrointestinal tract is where the virus hides, and niclosamide could eradicate Covid-19 from the GI tract.

William H. Lewis

Chair & CEO
INSMED

> We went from a one-product company, with one approval in one area, to a three-program story with global reach, each with the potential to be the cornerstone of therapy in the respective diseases they address.

What made 2020 such a transformative year for Insmed?
2020 was the most significant year in our history. We went from a one-product company, with one approval in one area, to a three-program story with global reach, each with the potential to be the cornerstone of therapy in the respective diseases they address. Treprostinil palmitil inhalation powder (TPIP) is a novel drug that we believe will have the potential for disease modifying impact for pulmonary hypertension. Our second program, brensocatib, is in phase three development for the treatment of, initially, bronchiectasis, but it is a drug that represents the exploitation of a new pathway for the treatment of neutrophil mediated diseases. Our third program ARIKAYCE was the first ever approved therapy for the treatment of refractory nontuberculous mycobacterial lung disease (NTM) caused by Mycobacterium avium complex (MAC).

What unmet medical need is ARIKAYCE filling for NTM patients?
There had not been any development work in NTM for decades, prior to the development of our drug, which is a drug-device combination. Patients inhale the drug to deliver it locally to the lung to try to fight their NTM infection. The infection is serious and difficult to treat, which is why nobody had secured an approved product before. We decided to position our drug to be used on patients who have failed every other therapy. The impact of the drug is the potential eradication of evidence of bacteria from the patient. ARIKAYCE is a very impactful drug, going after a very challenging disease state, and the results have been gratifying because we saw almost a third of the patients with no evidence of infection after treatment with our drug in our phase three trial.

What role does the Orphan Drug Act play in incentivizing these therapies?
There has been an immense amount of advance as a result of the Orphan Drug Act focusing industry's attention on less known diseases that affect fewer than 200,000 people in the US. NTM is one such disease. It is common in that pathogens are ubiquitous in the environment, so we are all exposed to it, but only a very small group of people develop it into an indolent disease that requires treatment. It numbers around 100,000 patients in the US, of which we went after the most severe, the refractory population, which numbers between 12,000 and 17,000.

Can you provide an update on the progress Brensocatib is making?
Brensocatib is our DPP1 inhibitor. It is in phase three right now for the treatment of non-CF bronchiectasis, another pulmonary disease without any approved treatment. Last year, one of the key elements of our transformation was the success of our phase two program with this. It hit its primary endpoint, which was a reduction in pulmonary exacerbations, reducing the risk of exacerbation by about 40% over six months, compared with placebo. The phase three trial is now running, and we think we unlocked a pathway that provides the opportunity for this medicine to be used in a number of diseases, including cystic fibrosis. We were granted breakthrough therapy designation from the FDA and prime designation from the European Union, both for the treatment of non-CF bronchiectasis, and the results of the phase two study were published in the New England Journal of Medicine, which is unusual for Phase 2 data. All of these things signal the promise of this medicine.

What is Insmed's approach to pricing?
Pricing is ultimately a collective bargain to find ways to bring innovation forward to serve humanity around the world. When we talk about pricing we have to remember, there are several things going on, the first being the scope of impact a medicine has on a patient. For example, ARIKAYCE has the potential to eradicate the disease. If you consider our investment ecosystem, we have other innovations we are making to try to advance other medicines including further innovation in the treatment of NTM. ARIKAYCE supports that through the process of setting a price and securing reimbursement. Most importantly, whenever you are in this industry, you cannot talk about price without mentioning access. Every company needs to remain committed to ensuring that every appropriate patient has access to the medicine. ■

Eric Ostertag

CEO
POSEIDA THERAPEUTICS

How have you seen the field of gene therapy evolve over the course of your career?
Today we are closer than ever to my lifelong dream: to create cell and gene therapies that do not just have the possibility of prolonging life but could potentially provide single treatment cures for cancer and other genetic diseases.
The first big trend has been to go to completely non-viral genetic engineering technologies. To do that, you need two components. One, you have to replace the ability to get into the cell, which the virus normally would do via infection. We think the non-viral solution to getting into cells will be nanoparticles. These make up an artificial shell that encapsulates the therapeutic transgene and will get into specific cells of a person.
That is only half the story, because you would also want that therapeutic transgene to go into the patient's genome and result in long-term stable expression. If you can achieve this, you can then think about gene therapy as a potential single treatment cure. However, just delivering DNA into the cell cytoplasm would not do that. It would be a transient approach, which is where most of our competitors are right now. At Poseida, we solve that half of the problem by using a non-viral DNA delivery technology called a transposon that we refer to as Super piggyBac (SPB), which can stably integrate a therapeutic transgene into a patient's genome and thereby create a potential single treatment cure. If you combine these two things, a nanoparticle and SPB, you have created a substitute for a virus but with none of the problems that we had with viruses for gene therapy over the last 25 years.
The other big advance is the advent of gene editing. Now you can edit as little as a single nucleotide in the genome. We invented a site-specific gene-editing system called Cas-CLOVER, which is easy to use and low cost, similar to CRISPR, but it does not have any of the unwanted and potentially unsafe off target mutations. ■

Geoff MacKay

President and CEO
AVROBIO

What are the indications that we are entering into a golden age for gene therapy?
Within a decade or so, I believe that we have the potential to transform the lives of many people living with serious genetic disorders.
One key challenge is matching genetic diseases with the right delivery system. We work exclusively with ex vivo lentiviral gene therapies for lysosomal disorders, which are designed to have a unique ability to deliver therapeutic proteins from head to toe – potentially including the brain and the spinal cord as well as peripheral tissues. Another important challenge for gene therapies is that of scale. It's not easy to manufacture cell and gene therapies.

How does AVROBIO's plato platform help with scalability?
plato is our proprietary platform designed to optimize the safety, potency and durability of our gene therapies while potentially enabling rapid scale-up and commercialization. Each of our product candidates uses a four-plasmid vector system. Three of the four plasmids used in every vector are the same; one plasmid is unique to the disease indication. The beauty of plato is that as you move from one indication to another, you simply change out one plasmid.

How is AVROBIO attempting to redefine the current standard of care for lysosomal disorders?
We start with the patient's own hematopoietic stem cells, use a lentiviral vector to transduce them in the lab to insert a therapeutic gene, and then re-infuse them into the patient, where they can engraft in the bone marrow. Following engraftment, these cells are expected to produce generations of daughter cells, each carrying a copy or several copies of the therapeutic gene. The patient should have trillions of genetically corrected cells in circulation, each expressing the therapeutic enzyme needed to keep the lysosomes functioning properly. Through this approach, we hope to bathe all tissues and cells in the necessary enzyme 24/7.
Importantly, our lentiviral approach is designed to enable treated cells to cross the blood-brain barrier and engraft in the brain and central nervous system to potentially address the cognitive symptoms that are so important with many lysosomal disorders. ■

Amit Munshi

President & CEO
ARENA PHARMACEUTICALS

What makes Arena's portfolio attractive today?
We are progressing four compounds and eight indications in three therapeutic areas. UC 12 and UC 52 are phase three trials for Etrasimod in ulcerative colitis (UC) reading out in the first quarter of 2022. That will be a gating event for us to begin to build our commercial infrastructure and begin to become a global commercial pharmaceutical company.

Can you provide an update on the GLADIATOR trial?
GLADIATOR is the first prospective study looking at moderate UC patients. There are 150,000 moderate UC patients in the US. These are prime candidates for receiving a once a day oral that has the profile of Etrasimod. If we are successful in our studies, the GLADIATOR program is going to be a critical leg of the stool in order to allow us to address a much larger market population.

What differentiates Etrasimod from other therapies in development for UC?
Etrasimod does not require a titration schedule, has a very fast on rate, we are three times faster than Ozanimod in terms of off rate, with patients returning to normal within a week if you withdraw the drug. Finally, we showed an efficacy signal that is almost two times that of Ozanimod, based off of results in phase 2 – with the caveat that these are cross-trial comparisons.

What is Arena's approach to navigating economic cycles, and how has the current boom in biotech financing impacted recruitment of talent?
Capital has been available for biotech assets and science has moved forward at a breakneck speed. What is missing broadly in biotech is human capital. You cannot triple the number of publicly traded biotech companies and continue building teams. There is simply not enough talent out there. Our biggest challenge is continuing to scale and grow the company while attracting high quality talent. ■

Paula Brown Stafford

President and CEO
NOVAN

What is the vision you are currently pursuing for Novan?
Our vision is to be the world's leading nitric oxide-based science, technology and clinical translation company. Our proprietary technology came out of the University of North Carolina Chapel Hill in 2008, and we currently have a pipeline consisting of multiple drug product candidates. We are determined to harness the power of this technology to develop safe and efficacious therapies.

What is unique about Novan's Nitricil technology platform?
Nitric oxide is a heavily researched molecule, but there have been challenges associated with controlling the release of the gas and the ability to stabilize and store it. That is what Novan has been able to do with our NO Platform. We store nitric oxide on a polysiloxane backbone, using our proprietary Nitricil technology, and then we can tune the timing and duration of the NO release via our formulation science. This two-part component requires a hydrogen donor source to begin the release process, which is tuned based on specific formulations. The formulation science is such that when the donor source mixes with nitric oxide that is sitting on that backbone, it launches and becomes active. This is why the technology is proprietary and novel. Each of our candidates are based on this technology.

Can you outline the unmet medical need Novan is addressing for Molluscum patients?
Molluscum is highly contagious and it can spread to become as many as 100 lesions. When you have lesions all over your body the only thing you can do is wait or request an in-office procedure. On average, it takes 13 months for it to resolve on its own. Our product candidate could allow these patients to put the medication on their lesions every morning for up to 12 weeks and it could give them a solution far quicker than if they were waiting for it to resolve on its own. ■

Josep Bassaganya-Riera

Chairman, President and CEO
LANDOS BIOPHARMA

What was your inspiration for founding Landos Biopharma?
Landos Biopharma was the culmination of over 20 years of research in the field of nutritional immunology. I founded several companies of which one, BioTherapeutics, had three separate business units. A main focus was on nutraceuticals. We had an AI-based computational engine which helped add layers of efficiency in how we design products. In 2016, we added an emergent therapeutic program, which built on these computational capabilities and was starting to leverage some of the targets that we identified from a nutraceutical perspective.
I soon realized that it did not make sense to keep these different business units under the same roof and, in January 2017, I created Landos. The focus of the company was going to be only therapeutic development with the mission to develop safer and more effective therapeutics for autoimmune diseases.
The autoimmune indication market is huge and is expected to be US$153 billion by 2025. Our initial autoimmune indication focus was on Crohn's disease and ulcerative colitis (UC), two diseases with an extremely large unmet medical need and a multi-million dollar market. We are focusing on targets at the intersection of immunity and metabolism, leveraging our AI-based integrated computational platform to identify important new molecular targets. In a short time, we have built a robust pipeline which has seven novel clinical and preclinical candidates across various areas of unmet medical need through three pathways.
Our mission is articulated around four computational pillars, the first one being targeting the intersection of immunity and metabolism. Secondly, we are focused on developing drugs that minimize safety concerns, which are extremely prevalent in the autoimmune space. The third pillar is to restore immune tolerance, and the only way we can achieve this is through our fourth pillar: focusing on novel mechanisms of action. What differentiates Landos is that we are grounded in novel mechanisms, which provide advantages in terms of improving the treatment paradigm, modulating multiple critical pathways through a single target, and cost efficiencies. We have leveraged a powerful AI-based platform into having a phase-3 ready asset for UC, BT-11.

> **In a short time, we have built a robust pipeline that has seven novel clinical and preclinical candidates across various areas of unmet medical need through three pathways.**

How can the drugs in Landos' pipeline improve the standard of care in the autoimmune diseases space?
The UC and Crohn's disease markets are currently dominated by biologic drugs. Approximately 68% of the market is biologics that have generated sales of nearly US$19 billion in the US. The treatment paradigm for UC and Crohn's disease is a step-up approach and patients that are newly diagnosed start off with 5-ASA, a safer treatment, moving to TNF-a blockers, integrins or oral drugs such as Jak inhibitors or S1P1 modulators in more moderate and severe treatments as needed. There is currently a high density of drugs for moderate to severe states of disease in the market or in late-stage development. There are, however, several safety concerns with these drugs. The mild to moderately affected patient population represents approximately 64% of the overall addressable population, and thus a large portion of patients are unserved or underserved, and a unique opportunity to extend the current market.
There is a great necessity for drugs such as BT-11, which has a very benign safety profile and is very well tolerated. We believe that with our oral products we can enter the treatment paradigm after the first line therapies while competing with TNF-alpha blockers, so that we can capture patients earlier and avoid patients having to move into drugs that could have concerning side effects.

What is the vision for Landos over the next 3-5 years?
In four years, Landos has grown from an idea to a Phase 3-ready asset. We have a unique opportunity to take our BT-11 asset into commercialization. We believe that moving forward, we can convert Landos into a fully-integrated biotech company that not only has a very powerful R&D engine, but also a very robust commercial arm. ■

Bernat Olle

CEO
VEDANTA BIOSCIENCES

What was the inspiration behind establishing Vedanta Biosciences?
A few years ago, I was part of a private venture creation team at PureTech, who had funding to start projects in new areas of science. I became very interested in the human microbiome field because I had seen several interesting research publications, including some that suggested that immune system responses can be calibrated by microbes that live in the intestine. There was also research showing that the gut microbiota could influence how we resist infection and certain metabolic processes, such as how much energy we harvest from food and ultimately how much weight we gain. Around the same time, the NIH declared the Human Microbiome Project, where investments of public funds were made available for the cartographic work of establishing what bacteria live in the intestine and what they do. This work provided a foundation of knowledge that our industry has been built upon. I then thought it would be an interesting idea to explore establishing a company in this field and I reached out to academic researchers who had been doing, in my view, the pioneering work to help understand how microbes in the intestine shape immune responses. Together, we discussed what aspects of microbiome work we thought could make the biggest impact in medicine, analyzed many technologies, and ultimately formulated a vision for what would become Vedanta.
We decided to focus on how microbes in the intestine shape immune responses, and from a modality point of view, we focused on using defined consortia of bacteria. We can screen libraries of bacterial isolates just like a pharmaceutical company would screen their library of small molecules to identify the best potential bacterial components for a product, and then assemble them as a consortium. We found that if you pick the right combination of bacteria, you can consistently surpass the potency of any given individual bacterial strain.

> Our ultimate vision is to enable defined consortia of bacteria as a new drug modality, in the same way that Genentech enabled protein biologics and Alnylam enabled RNAi therapies as new modalities.

How does Vedanta's VE202 compare to Seres Therapeutics' SER-287?
VE202 is a standardized product. There is no donor step in VE202. We start from clonal cell banks of bacteria that are sitting in a freezer, which we then expand by fermentation to create a product that is always going to have the exact same composition, potency and dose. We can also make sure the drug does not carry any pathogens because we deliberately only include the specific bacteria that we want to allow in the product. Importantly, by producing the drug by fermentation, we can scale up the production to make as much as we need at a much lower cost of goods than a donor-derived procedure.

How do Vedanta's partnerships with BARDA and the Gates Foundation illustrate the scalability of defined consortia of bacteria?
BARDA and the Gates Foundation care about scalability, among other considerations. For a product to be considered for addition to the National Strategic Stockpile, or for use in the developing world, one has to imagine a path to produce a fairly large number of doses at a cost that is not prohibitive.
That is something that we believe we can do very effectively with our approach. We are the company that has pioneered this standardized product type of approach to the microbiome with defined consortia of bacteria.

What is your long term vision for Vedanta?
Our ultimate vision is to enable defined consortia of bacteria as a new drug modality, in the same way that Genentech enabled protein biologics and Alnylam enabled RNAitherapies as new modalities. Since inception, we have been relentlessly removing the technical risks involved in making the modality a reality: we first showed how to rationally select a drug candidate based on a defined bacterial consortium. We then developed the technical capabilities in-house to be able to manufacture GMP-grade defined consortia for use in human studies. Later, we conducted several PK-PD studies in humans to map out a rational way to select a dosing regimen for such a new modality. Now, we are testing the efficacy of these dosing regimens in patients in Phase 2 studies. All of those are logical steps to follow to remove the risks inherent in a new modality. We have applied the learnings across our pipeline, with multiple programs in infectious and immune diseases now in the clinic. ■

Advancing Oncology

PROGRESS BRINGS CURES INTO SIGHT

Since taking office in January, President Biden has referred to cancer, or "the C word", as the most frightening word in the English language. This sentiment comes from the personal experience of losing his son to a glioblastoma brain tumor. But the macro data also supports this view. According to the American Cancer Society, approximately 608,570 Americans are expected to die of cancer in 2021, which translates to 1,670 deaths per day. Cancer is the second most common cause of death in the US, exceeded only by heart disease. The financial burden of cancer is also severe. Cancer-related direct medical costs in the US were around US$200 billion in 2020, and are projected to increase to US$246 billion by 2030, based only on population growth and aging.
That said, the five-year relative survival rate for all cancers combined has increased substantially in US since the early 1960s, from 39% to 68% among white people, and from 27% to 63% among the black population. Such a transformation in outcomes has arrived through a combination of public-health measures, such as smoking education, improved healthcare such as earlier diagnosis, and novel pharmaceutical therapies. This trifecta has turned select diagnoses, once considered terminal, into chronic conditions. For example, most patients now diagnosed with multiple myeloma or prostate cancer will have mortality tied to conditions other than their cancer.
Because of the widespread pain the disease causes and enormity of its market size, oncology is a declared focus area for the 10 largest pharmaceutical companies, with an estimated 1,700 clinical compounds in development. This amounts to approximately one-third of the global clinical pipeline across all therapeutic areas.

Immuno-Oncology

One of the hottest areas of development in recent years has been in the immuno-oncology (I-O) space. Immunotherapies have transformed cancer treatments in the last decade, and that transformation is led by a class of drugs known as checkpoint inhibitors. In particular, Merck's Keytruda and OPDIVO from BMS are both considered checkpoint inhibitors, and they work by taking the so called brakes off the immune response. These drugs are incredibly successful, with Keytruda selling a billion dollars in monthly revenue. They are getting approved in multiple different types of solid tumors, which comprise about 90% of all cancers. However, they only work

in a minority of the patients that receive them. The reason is that their tumors are immunologically cold.

OncoSec has set out to solve this problem by introducing IL-12, a pro inflammatory signaling cytokine, contextually into the tumor microenvironment. This method has the ability to confirm if that tumor is immunologically suppressed, immunologically activated or active. They do this by coding IL-12 onto a DNA plasmid. By putting DNA plasmids into the tumor coded for IL-12 they get that DNA inside of cancer cells and other cells in the tumor. This process is done via gene electrotransfer. In outlining the benefits of this technique, OncoSec Medical president and CEO Daniel J. O'Connor explained: "We are not using an antibody or virus or bacteria to deliver DNA into cancer cells, we are using energy. As such, we do not have an issue with systemic toxicity… We do not want to supplant chemotherapy or radiotherapy side effects with immunotherapy side effects. We want to have a natural immune response that avoids cytotoxic consequences for the patient experience, and our way of delivering IL-12 is getting a lot closer to that big idea."

Many investors favor OncoSec's approach because, in comparison to other new therapies, it is cost effective. "If you look at autologous treatments that require the extraction of cells from a patient, manipulation of those cells in a cGMP facility, and then a one-to-one reintegration from treatment to patient it costs US$100,000. It can work, but it is expensive, and those costs must be paid eventually. That is why I favor our plasmid-based approach. Plasmids are very cost effective to make," said O'Connor.

Precision Medicine

Scientists have long known that cell therapy, which replaces diseased, faulty or missing cells with healthy versions, could open new horizons in medicine. Now, following a string of regulatory approvals and positive clinical trial data, there is growing optimism that they can be applied to a wide range of diseases. Blood cancers, specifically lymphoma and leukemia, are cell therapy's first breakthrough domain, thanks to innovations in Car-T therapy, which alters a patient's immune cells to make them better at fighting cancer. Building off of the earlier success of Gilead and Novartis, in March 2021, BMS and Bluebird Bio jointly received FDA approval for Abecma to treat patients with multiple myeloma who are unresponsive to four or more previous lines of therapy.

Although these cell and gene therapies will undoubtedly have a large impact on the market, cost and manufacturing pose a serious challenge. For example, Abecma will cost US$419,500 per dose. As Eric Ostertag, CEO of Poseida Therapeutics, described: "Right now, (CAR-T cell therapy) is mostly done by autologous or individualized therapies. If somebody gets cancer, you manufacture their cells and put them back into the patient. Consequently, it is a very expensive process; it is time consuming and the clinical trials are expensive and time consuming as well."

In response to these challenges, companies like Poseida are focusing on a fully allogeneic process, which means they will take cells from a healthy donor, manufacture them and then potentially give them "off the shelf" to many patients. That drops the cost of manufacturing while greatly expanding patient access.

One of the key issues is that most companies with CAR-T right now are only able to make somewhere between six to 12 doses from a single manufacturing run. With Poseida's "booster molecule" this process holds the potential to be much more scalable. "We have shown we can make hundreds of doses from a single manufacturing run and that takes the cost of manufacturing CAR-T from well over US$100,000 to just a few thousand dollars, putting it in the same range as a monoclonal antibody or a bispecific therapy," Ostertag affirmed.

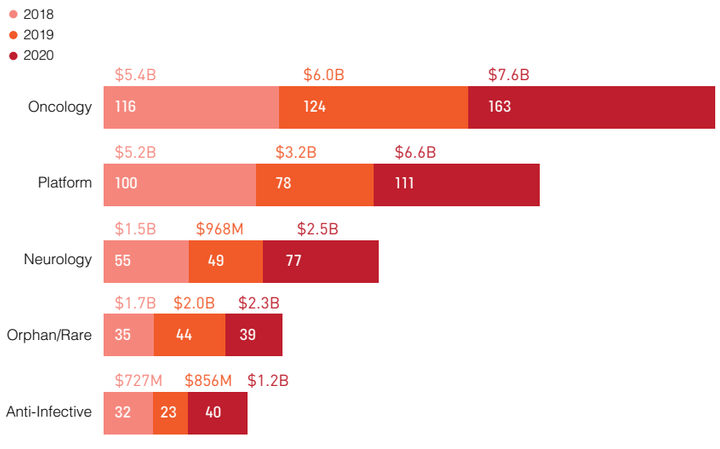
From Genetics to Epigenetics

Surrounding the DNA in all our cells are molecular systems that tell genes when to turn on or off. As researchers learn more about these so-called epigenetic mechanisms, they are increasingly looking to use them to modify problematic genes. Foghorn Therapeutics, which was incubated and funded by Flagship Pioneering, targets one aspect of epigenetics — chromatin winding — to try to treat first cancer, and then other disorders. Foghorn Therapeutics, based in Cambridge, Mass., was co-founded in 2016 by Cigall Kadoch, whose research into chromatin regulation defects in a rare childhood cancer laid the groundwork for the company's drug approach.

They soon brought on Adrian Gottschalk as president and CEO, who took the company public in a US$120 million IPO in October 2020. When asked what compelled him to leave Biogen to join Foghorn, Gottschalk replied: "50% of cancers have some sort of mutation

Biopharma Deals and Dollars by Top Indications

Source: Silicon Valley Bank

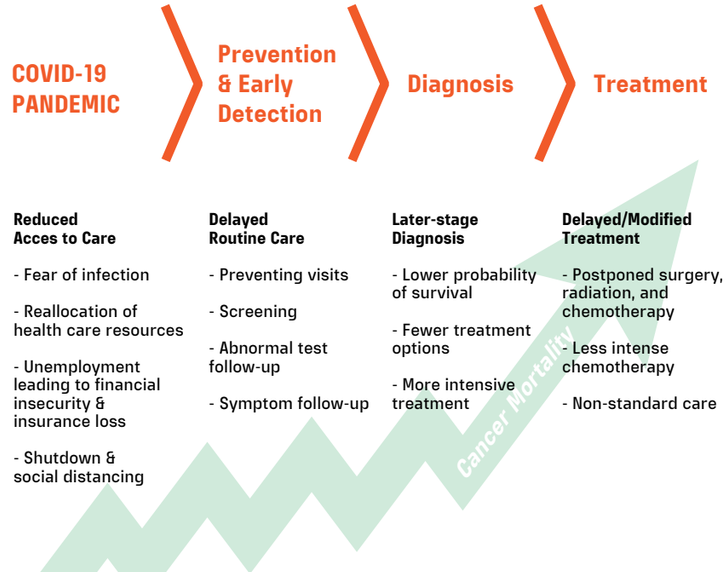


We see an opportunity for miRNAs as they can bind to several mRNAs at the same time to induce mRNA cleavage or inhibition of translation to functional proteins. What you see if you do transcriptomic analysis is that these small miRNAs bind to mRNAs across different signaling pathways... By intervening across different pathways at the same time and through dysregulation of multiple mRNAs at the same time, you potentially make it much more difficult for the tumor cell to develop resistance.

- Roel Schaapveld, CEO, InteRNA Technologies

Potential Impact of the COVID-19 Pandemic on Future Cancer Outcomes

Source: American Cancer Society, Inc., Surveillance Research



or breakdown associated with the chromatin regulatory system, meaning this biology is playing a central role in the disease state. I found it profound that you had a system that was orchestrating gene expression, got hijacked by cancer cells and could potentially be corrected in some way. It could have a big impact on cancer patients."

The company now has IND clearance for FHD-286 in both relapsed and refractory AML and metastatic uveal melanoma, and is currently initiating its first two clinical studies with initial data possible by the end of 2021.

Constellation Pharmaceuticals is another company incubated by a group of venture capital firms: The Column Group, Third Rock Ventures and Venrock, and is focused around epigenetics. They recognized that the potential for small molecule inhibitors to control gene expression through epigenetic mechanisms can be powerful in combating disease, and built their drug discovery engine to develop a pipeline around that thesis. While the company's lead candidate Pelabresib is indicated for Myelofibrosis, it also is developing a second generation EZH2 inhibitor called CPI-0209 and CPI-482, which is an LSD1 inhibitor. Constellation president and CEO Jigar Raythatha commented: "Discovery is our lifeblood. Everything that we have progressed into the clinic has been homegrown. This underscores our strategy to invest in translational science. CPI-482 has a significant effect on myeloid biology, which could help us move into adjacencies and complimentary spaces."

Covid Impact

Despite the vast potential of new therapies and diagnostics in development, the reality is that cancer rates are expected to spike substantially as a result of disruptions in research, screening, diagnosis and treatments. The priority for the medical battle against Covid-19 has necessarily been to tackle the crisis caused by the virus itself. But other aspects of human health face collateral damage on a huge scale from the pandemic, which will require governments to increase health spending even faster than previously planned for several years to come.

As Lancet Oncology said in its editorial on Covid one year on: "Covid-19 has had devastating effects on patients with cancer, with huge numbers of missed diagnoses and delayed treatments due to health systems under pressure and patients' reluctance to seek medical care."

Michael Kauffman, CEO of Karyopharm Therapeutics confirmed this observation via the impact of his company's rollout of XPOVIO for patients with multiple myeloma. He noted "Estimates are that between 30-70% of appointments in patients with active cancers were missed. When the history is written on this pandemic, I think we are going to see a lot of excess morbidity and mortality because of these missed appointments"

With this in mind, the next decade will be defined by continued effort to push the boundaries of what conditions are deemed "treatable." ■

Daniel J. O'Connor

President & CEO
ONCOSEC MEDICAL INCORPORATED

Can you provide an overview of the key events that drove OncoSec's market outperformance in 2020?
There was a convergence of good things that occurred for OncoSec in 2020, and it centered upon a preliminary data release we provided on KEYNOTE-696 at the Society for Immunotherapy of Cancer (SITC) annual meeting where we reported the tumor shrinkage response for the first 54 patients participating in the trial study. People appreciated the data as showing that the study was on track to meet its primary endpoint, which is a 20% response rate by BICR (blinded independent central review). The second positive item was closing a deal to begin collaboration with China Grand Pharmaceuticals (CGP) and Sirtex; two powerful drug development companies that we expect will flourish over time. The deal also provided OncoSec with US$30 million of capital to continue our ongoing and future clinical trials. Over the course of the year, we continued to raise capital binging in another US$15 million in August.
We want to give life to the concept, underpinning the paradigm of cancer immunotherapy, which is to use the body's natural immune response. We want to have a natural immune response that avoids cytotoxic consequences for the patient experience, and our way of delivering IL-12 is getting a lot closer to that big idea.

One of the problems with the biology of tumors is they are considered to be immunologically cold and we know checkpoints do not work well in this case. What is Oncosec's approach to solve this problem?
First, it is important to understand what is happening vis-a-vis the checkpoint. In our study we are evaluating patients who used Keytruda or OPDIVO. These are both approved drugs in first line, late-stage metastatic melanoma or skin cancer. These are checkpoint inhibitors and they are monoclonal antibodies (MAB's). In the case of Keytruda, it is a blocking antibody engineered to look like a protein that is capable of turning a T-cell off. Keytruda is an antibody that is able to mimic the protein and fit into that receptor, like gum in a lock. If the gum is in the lock, the natural protein cannot hit the receptor and turn the T-cell off, so it competitively inhibits the protein that would naturally be suppressive for turning the T-cell off.
Keytruda blocks the antibody that competitively inhibits the natural protein, which is otherwise immunosuppressant. Therefore, when a T cell then traffics to the tumor, it is not able to do its killing job because the tumor itself is immunosuppressed. Keytruda works well in hot tumors because there are T-cells that are kept activated through the blocking antibody trafficked to the tumor and can get in and do their killing job because the tumor itself is not immunologically suppressed. However, the majority of patients have some level of immunosuppression occurring in their tumor. IL-12 is a pro inflammatory signaling cytokine, and, as a signaler of inflammation, reintroducing IL-12 contextually into the tumor microenvironment has the ability to confirm if that tumor is immunologically suppressed, immunologically activated or active. We do that by coding IL-12 onto a DNA plasmid. By putting DNA plasmids into the tumor coded for IL-12 we are getting that DNA inside of cancer cells and other cells contextually located in the tumor. We are doing that using energy, which is why we call it gene electrotransfer. That DNA medicine is our way of causing the DNA plasmid to be put inside of the cancer cell, and that happens by the millions.

> **We want to have a natural immune response that avoids cytotoxic consequences for the patient experience, and our way of delivering IL-12 is getting a lot closer to that big idea.**

What are the main costs associated with developing cancer immunotherapy drugs?
The reality is that a lot of the newer techniques in development are expensive. Therefore, developing a system that is cost effective from the start is a consideration. That is why I favor our plasmid-based approach. Plasmids are very cost effective to make. ■

Jigar Raythatha

President & CEO
CONSTELLATION PHARMACEUTICALS

What science is Constellation Pharmaceuticals pursuing?
Constellation was started by a group of venture capital firms around the area of epigenetics. They recognized that the potential for small molecule inhibitors to control gene expression through epigenetic mechanisms can be powerful in combating disease, so my first iteration with Constellation was about building an extensive discovery platform. This helped us identify novel development candidates. In thinking about the diseases in which we could make the most impact, we realized it was not in the areas where we saw initial activity in the clinic, so we pivoted to identify novel applications and supplement that with translational science information.

What is Constellations's approach to discovery, and how do you think creatively about development strategies?
Discovery is our lifeblood. Everything that we have progressed into the clinic has been homegrown. We recently nominated a new development stage candidate - CPI-482, which is an LSD1 inhibitor. This underscores our strategy toward investment in translational science. CPI-482 has a significant effect on myeloid biology, which could help us move into adjacencies and complimentary spaces to pelabresib.

What is driving interest in Constellation from public markets investors?
The enthusiasm for Constellation is driven largely by the potential for our lead program today. Myelofibrosis is very exciting for a multitude of reasons. There is high unmet need, a reasonable number of patients and treatment typically is needed for years. This translates into a very big opportunity for us as a company and our shareholders. I think a lot of the excitement from our investors was generated when they dug into the data that we presented, and they see pelabresib as a game changer, initially in myelofibrosis but then there is potential beyond that. Our discovery engine also fuels future value generating potential that we look to unlock for our investors. ■

Roel Schaapveld

CEO
INTERNA TECHNOLOGIES

Can you explain the promise microRNA therapeutics hold for treating multi gene diseases like cancer?
We see an opportunity for miRNAs, as they can bind to several mRNAs at the same time to induce mRNA cleavage or inhibition of translation to functional proteins. What you see if you do transcriptomic analysis is that these small miRNAs bind to mRNAs across different signaling pathways. These mRNAs that are regulated by one miRNA are connected across pathways, so in that respect there is potential for higher efficacy, plus a decreased chance of developing resistance.

What makes InteRNA's approach to miRNA unique?
The different approach we took is that the company had already identified novel miRNAs at that time using deep sequencing and bioinformatics. We cloned the precursor molecules in a lentivector system to allow for high throughput functional genomics screening in cell-based assays. That is a non-biased genomics approach where you look to phenotypic readouts after you have transfected the tumor cell with a specific miRNA out of the library that we employ. Through these non-biased screens, we were able to pick up hits and we were able to confirm them with synthetic molecules. Therefore, once we make synthetic mimics of miRNA or synthetic antimiR's of miRNA, we were able to reproduce results in cell-based assays that we saw in the functional screens.
We then built a patent portfolio around them and took the validation further, expanding the cell line panel and extending the number of assays. After that we had to figure out the important step of transition from in vitro to in vivo. We were then able to generate preclinical proof of concepts in different mouse models, and we were able to build a preclinical product pipeline, with our first candidate recently entering the clinic. We have now made the transition from a platform company to a product company and from a preclinical company to a clinical company. ■

Michael Kauffman

Co-Founder and Former CEO
KARYOPHARM THERAPEUTICS

What were the key scientific insights that Karyopharm was founded on?
I co-founded Karyopharm along with my wife, Sharon Shacham in 2008. Our inspiration was derived from her scientific insight, which ran counter to the prevailing focus on genetically defined cancers and typically small populations where you can show good effects, but they are only applicable to a small minority of patients. She wanted to work on the hallmarks of cancer and how to attack basic underlying mechanisms of cancer. Eventually she settled on the idea of tumor suppressor proteins. Her insight was that every time she read about one of these tumor suppressors, she found out that it was kicked out of the nucleus by a single chaperone or carrier protein, and it was always exportin 1. If you block this single protein, you can restore tumor suppressor proteins to the nucleus, because they get in, but if you block this exporter, they cannot leave. This would therefore be sufficient to activate their function, which is to kill cells with DNA damage. We are able to restore the tumor suppressor proteins to the nucleus where they can kill cancer cells, and they kill some cancer cells better than others. Our first approvals are in multiple myeloma and lymphoma, but the drug has general applicability across essentially any cancer.

What kind of response rates are you seeing from XPOVIO?
In myeloma we can get responses between 50-90%. In a recent, small combination study in the front-line setting for patients with diffuse large B-cell lymphoma, all of the patients have responded. In lung cancer we are doing a study where we will report out later this year some responses in patients with chemotherapy and immunotherapy refractory lung cancer, and in melanoma we reported last year from the MD Anderson Cancer Center a 54% response rate in combination with KEYTUDA, which is an immunotherapy. ■

Adrian Gottschalk

President & CEO
FOGHORN THERAPEUTICS

What is the founding story of Foghorn Therapeutics?
For a long time, the biology of the chromatin regulatory system was thought to play a housekeeping role within the cell. It was there but not well understood and not thought to be relevant in different diseases. Over the last decade, we realized this was far from the truth. This biology is playing a central role in orchestrating, controlling and regulating gene expression. Consequently, when you dig into it, you start discovering that it is implicated in a wide range of diseases. It is a greenfield opportunity that holds tremendous promise – Foghorn is now starting to realize some of that potential.

Can you provide an overview of Foghorn's Gene Traffic Control Platform and how it enables new target identification and validation?
Our scientific approach starts with the underlying genetics. Mutations occur in the biological machinery or in the cancer cell, and in some cases they are dependent on the chromatin regulatory system for survival, and therefore effectively impact gene expression. Once we have figured out the mutation location, we can then use tools like CRISPR to validate if we hit the specific target.
The other part of our platform has the ability to produce the different components of this chromatin regulatory system. There are two principal components that we are focused on; chromatin remodeling complexes and transcription factors. The complexes are multi assemblies of proteins and contain a motor, which serves the principal purpose of localizing onto chromatin (a compressed form of DNA) and unpacking it (going from DNA to RNA to protein). We are also able to study and understand the interaction of chromatin remodeling complexes with transcription factors – these are homing beacons that localize the complex to the right location to ensure that the appropriate gene is opened and expressed. If this process goes awry, it can result in pretty serious diseases like cancer and others. ■

Commercializing Neuroscience

SOLVING THE THERAPEUTIC DROUGHT

Of the longstanding technical difficulties in the drug development business, few have proven more intractable than crossing the blood brain barrier – evolution's elegant system designed to protect the brain from harmful chemicals. A molecule must cross this barrier in order to effectively treat some of the world's most devastating neurological conditions, including ALS, Parkinson's and Alzheimer's.
The failure rate for drugs targeting diseases of the central nervous system (CNS) has been dauntingly high. Over the past 20 years, most drugs have been based on the "amyloid hypothesis," which began with a simple observation: Alzheimer's patients have an unusual buildup of the protein amyloid in their brains. Thus, drugs that prevent or remove the amyloid should slow the onset of dementia. Roche's gantenerumab and Eli Lilly's solanezumab are just a few of the more than 100 potential Alzheimer's drugs that have flopped in pursuit of a solution.
The prevalence of failure in treating neurological diseases is a testament to their unique challenges. Uncertain diagnoses, long progressive burdens of disease, multiple etiologies and complicated clinical trials are just a few factors that are impeding success. Given the history of failure it may seem that you would have to be either stupid, crazy or charitable to invest in this space. However, given macro and societal drivers, such as the global rise in the incidence of mental illness and the aging of the population, particularly in western societies, the payoff could be enormous.
An effective drug against Alzheimer's disease, for example, would be a blessing for millions while also being hugely profitable for the company that invented it. Hence the excitement over any promising trial result, such as Lilly's donanemab, and the intense interest in the FDA's decision on Biogen's aducanumab. According to Bernstein, US sales could amount to as much as US$50 billion a year for an effective Alzheimer's treatment.
This has led a barrage of contrarian investors willing to fuel entrepreneurs to discover and develop novel therapeutic strategies across a range of neurologic conditions. There are now new ways of thinking about neurologic diseases, informed by human genetics and a better understanding of the brain, that are emerging out of basic and clinical research and they are very encouraging. These offer new paths to develop targeted medicines in specific subsets of patients.
Swiss-based AC Immune is one company working to pioneer advancements in personalized therapies for CNS diseases. The company's co-founder and CEO, Andrea Pfeifer, noted: "We are reaching precision medicine in the neuro space. Precision medicine is based on the expression of misfolded proteins in the brain. We can look in the brain and dictate if you need an alpha synuclein or tau-targeted therapy."
This represents a shift in recognizing that Beta-amyloid is just one protein that can mis-fold in the brain. Others, such as tau or alpha-synuclein, could hold clues to deciphering how Alzheimer's disease develops in the aging brain.
Tau, in particular, has intrigued many, earning recognition as another characteristic mark of Alzheimer's disease. Tangled clumps of the protein can stretch across regions of the brain, and its presence is correlated with worse cognition. Up to this point, the field could only diagnose Alzheimer's when clinical symptoms were observed. This is a huge disadvantage akin to closing the barn door after the cows have left, because we now know that, by the time a patient has observable clinical symptoms, a lot of the neurons are already dead (estimates are that 70% of neurons are dead). The key then is to intervene when you still have all neurons intact. But up until today, this was not possible because there was no diagnostic means to identify people at risk. This has been one of the key developments over the past two years. We can now identify markers, such as phospho-tau 181 or phospho-tau 217, which allow you to identify people at risk, and begin treatment early on in the disease progression.
As an example, when you look at cardiovascular disease, a person goes to the doctor, gets checked for cholesterol and, if they have high cholesterol, then the doctor prescribes statins. The statins do not really treat heart disease but prevent it. There is now a recognition that risk markers for Alzheimer's disease appear 10-20 years before the disease starts. By identifying these factors early on, a patient could receive a vaccine because it costs very little, it works for a long time and people would not lose their neurons, which is absolutely required in order to prevent the onset of the disease. This is where the field is headed today. Pfeifer continued: "This is precision medicine, which of course means specificity. It means safety, because you do not treat for something which you do not have, and it is cost effective because you do not treat something which costs a lot of money and does not really help you."

Combination's coming

The idea that developing combination therapies spanning several misfolded proteins rather than focusing on a single target will be more effective is gaining in popularity, and it is something that Trevor P. Castor, president and CEO of Aphios, has been pursuing for several years. He points to lessons we can take from the progression of HIV treatment. "Combinations allow us to have therapeutic solutions, whereas a single therapy may not work. Case in point is in HIV. There was a very high amount of single therapy failures caused by resistance being developed by HIV mutations, and it was a problem until Ho came up with the idea to use a triple drug therapy to prevent the virus from mutating," said Castor.
Combination therapy, the basis for current antiretroviral therapy in the HIV world, is what made HIV a chronic disease rather than a killing disease, and, according to

Neuropsychiatric drug discovery has seen more money flow into it in 2020 than ever before and almost double 2019, both in terms of institutional investment and partnering. I think it was inevitable that we would see a resurgence of interest in CNS disorders as these are severely disabling conditions with poor or no available treatments that impact huge numbers of people worldwide.

- Emer Leahy, President & CEO, PsychoGenics

Castor: "The problem in neurodegenerative diseases like Alzheimer's is that we have not gotten any single therapies which have been effective in either suppressing or curing the disease. People ask, why use a combination therapy when we have not gotten the single therapy to work? The problem with a single therapy is that you hit only one target in a very complex biological system. For example, you inhibit one enzyme like beta secretase, and alpha secretase pops up as a contributing factor to Alzheimer's disease. It is important to start thinking about how we can combine therapies that can impact different pathways simultaneously in treating Alzheimer's disease."

On the back of this thesis, Aphios was granted a patent in 2020, titled "Combination Therapeutics and Methods for the Treatment of Neurodegenerative and Other Diseases." The company's findings were that the combination of Bryostatin-1 and retinoic acid is not merely additive to increase α-secretase, but synergistic, wherein the Bryostatin-1 and retinoic acid interact to form greatly elevated levels of α-secretase to make the treatment of neurodegenerative diseases more effective.

If you fund it they will come

A huge element of this expansion of basic neuroscience understanding has come from the explosion in National Institute of Health (NIH) funding for neuroscience in the first decade of the 2000s. In the 1990s, the NIH channeled US$954 million into neurology research. In the 2000s, this number spiked to over US$8 billion. This was a larger increase than any other therapeutic area and has created a wave of insights a decade later that we are in the process of translating into new therapies. Funding for the disease continues to increase dramatically, with NIA's support climbing more than fourfold between 2013 and 2019. For fiscal year '21, Alzheimer's research rose to US$3.1 billion

Neuropsychiatry

In neuropsychiatry there is also an abundance of companies thinking more outside of the box. For decades, the focus was on retreads of blocking dopamine in psychosis and modulating monoamines like serotonin, dopamine and norepinephrine in depression. Now there are many more new targets. And that is largely coming from early stage biotech rather than traditional large pharma who might be biased and set in their ways of thinking about things through a certain biological paradigm.

Emer Leahy, president and CEO of PsychoGenics, recognized: "Target-driven approaches to neuropsychiatric drug discovery, which biopharmaceutical companies were pursuing to the exclusion of other approaches, had serious flaws; confirmed decades later by the sparsity of new first-in-class treatments. We pioneered an alternative phenotypic approach that captures hundreds-of-thousands of behavioral and physiological datapoints from mice and employs machine learning to predict therapeutic applications for novel compounds."

This target-agnostic approach has thus far shown promise, as it has delivered novel first-in-class clinical compounds, such as SEP-363856, with improved efficacy and side effect profiles for unmet neuropsychiatric needs such as Schizophrenia.

Driving the advancement of PsychoGenics' pipeline is its robust CRO business that continues to grow on the back of the expanding number of newly formed, venture backed companies requesting its services. However, the future growth of the company will depend on the clinical success of SEP-363856, which could validate the company's AI-driven discovery platforms.

Brain Game

In addition to advancements in the diseased brain, those with cognitive impairments are also receiving renewed attention. There is a movement afoot that says the immersive power of video games can be harnessed not only to entertain, but to enhance cognitive abilities. While educational games have been around a long time, some neuroscientists believe that games can act as therapeutic tools against conditions like ADHD and autism. The field took a major step forward in June of 2020, when Akili Interactive was awarded FDA clearance for its EndeavorRx, a "digital therapeutic" developed to treat ADHD through a video game experience. The regulatory decision makes the Boston company's product the first prescription therapy that comes in the form of a video game. When asked how the path forward may differ from that of a traditional pharma company, Akili co-founder and CEO Eddie Martucci emphasized: "Realizing the full potential of digital therapeutics to transform the patient experience requires imagination and creativity. DTx have the bandwidth to span multiple audiences and be easily accessible for download via a mobile device, which positions companies with innovative technologies to support more patients. We do DTx a disservice by applying a pharma model to this new industry."

As a result, the company is developing a purpose-built distribution model designed specifically for digital therapeutics that can support the level of patient engagement and rapid product development this new category of medicine has the capability of delivering. ■

Trevor P. Castor

President & CEO
APHIOS

Can you speak to how Aphios' Critical Fluid Inactivation (CFI) technology can help provide convalescent plasma as a disease treatment?

Aphios has been conducting research in this area for several years now, but in 2020 we accelerated our research program to clear convalescent plasma of potential viruses including coronavirus. The key is to utilize the technology for units of plasma so it is traceable, rather than pool plasma. Currently, we are designing equipment to deploy in hospitals, as well as remote settings around the world.

People in West Africa may be facing an Ebola outbreak, where you may have areas of localized flare-up. When you have patients who are recovered, you can treat the plasma from that patient, and reintroduce it into a patient who has been infected with the disease. This can act as a very quick therapeutic, rather than having to develop a new monoclonal antibody or vaccine.

Aside from CFI, what area of the business has been the biggest focus for Aphios over the past year?

An area that is of keen interest remains cannabis and cannabis-related products. We are focused on establishing partnerships to develop therapeutics for cannabidiol in the area of cancer-induced peripheral neuropathic pain (CIPNP), as well as substance use disorder (SUD) and opioid use disorder (OUD).

Do you see the changing of the political guard in the US as being more encouraging of those pursuing the therapeutic potential of cannabis?

The regulatory barriers to development have been challenging from a combination of the Drug Enforcement Agency, FDA and NIH. They all work together to regulate the utilization of cannabis-based products on a national basis. I think with the new administration there will be some deregulation, which will allow more research, more clinical development, and more products in the marketplace.

Another trend we are anticipating is that as a result of more cannabis use being permitted in different states, there is going to be a greater focus on addiction prevention. You are inevitably going to get a significant portion of the population who is addicted to marijuana. Aphios is investigating this as a potential therapeutic target area.

We are very interested in neuropathic pain, for which more than 50% of cancer patients suffer. You have no interdictions and no therapeutic modalities that work right now. Anecdotally CBD works, but it is an acute-type response, and we are planning to move forward with our program to do more on nanoencapsulation to sustain the release of CBD in the body. This will give patients a better therapeutic effect.

This past year, you received a patent on "Combination therapeutics and methods for the treatment of neurodegenerative diseases." What is the significance of your research on this topic?

We believe that for most modalities, combination therapeutics are needed. I call it a whack-a-mole theory. As you whack one particular pathway, another pathway pops up. Combinations allow us to have therapeutic solutions, whereas a single therapy may not work. Case in point is in HIV. There was a very high amount of single therapy failures caused by resistance being developed by HIV mutations until Ho came up with the idea to use a triple drug therapy to prevent the virus from mutating. That combination therapy is what made HIV a chronic disease rather than a killing disease.

The problem with a single therapy is that you hit only one target in a very complex biological system. For example, you inhibit one enzyme like beta secretase, and alpha secretase pops up as a contributing factor to Alzheimer's disease. It is important to start thinking about how we can combine therapies that can impact different pathways simultaneously in treating Alzheimer's disease.

What are some key milestones Aphios is looking to achieve in 2021?

One of our key goals is to conduct clinical trials, which are capital intensive. Therefore, we have an A strategy and a B strategy for fundraising. Our preferred strategy is to do a mezzanine round of financing and then an IPO to generate the capital necessary to execute clinical trials. Our plan B is to spin off companies, special purpose vehicles (SPVs), which are focused on both product or technology in different areas of our platform or product pipeline. ■

We are focused on establishing partnerships to develop therapeutics for cannabidiol in the area of cancer-induced peripheral neuropathic pain (CIPNP), as well as substance use disorder (SUD) and opioid use disorder (OUD).

Andrea Pfeifer

Co-Founder & CEO
AC IMMUNE

What was your inspiration for founding AC Immune?
I noticed that in the case of Alzheimer's and Parkinson's, it is always the case that there is a natural protein, and this protein changes its structure and becomes pathological. There is no mutation involved. Nobody knows why the structural change is happening. When you have this structural change, these proteins aggregate, so we speak about misfolding as a first step, then aggregation. The problematic part is that the only difference between a normal protein and a patient's protein is the structure, or the misfolding. When we started out, the key question was how can you generate an antibody or a vaccine which allows you to only select the misfolded pathological protein? This is why our platforms are so important. When I was contacted by the four scientific founders, these scientists convinced me that their technology, which became the platforms we use today, has the capability to generate antibodies, vaccines and small molecules that can only target the pathological protein, but not the normal one. When you look at our Tau vaccine data that we published in our clinical Phase Ib/IIa trial, more than 90% of the antigen response goes to the pathological form. If you do continued injections in people every 12-18 months, you still get the selection for pathological Tau. It is all built around misfolded proteins in the brain, and they aggregate in the neurons or extra-cellularly and kill the neurons. Today, we know Tau is involved in Alzheimer's. We also know alpha synuclein is involved, but the principle is always the same. This is why you need specific platforms and technologies to recognize the difference between normal and pathological.

> I think we are reaching the stage now where brain diseases become reachable because we can finally look into the brain.

What makes a vaccine-based approach appropriate for targeting Tau?
It was extremely difficult to make a vaccine because the immune system of older people is not very active and most do not generate strong antibody responses. This was preventing the field from moving into vaccines addressing neurodegenerative diseases. With our technology we have achieved that, which means you can now potentially prevent the disease. So far, we could only diagnose Alzheimer's when we saw clinical symptoms, but when you have clinical symptoms, a lot of the neurons are already dead. The trick is that you should intervene when you still have all the neurons intact, and this is before you see clinical symptoms. Up until today, this was not possible because we did not have the diagnostic means to identify people at risk. We can now identify markers such as pathological phospho-tau 181 or phospho-tau 217, which allow you to identify people at risk.
We see risk markers for Alzheimer's disease appearing 10-20 years before the disease starts. When we identify these factors, a patient could receive a vaccine and would not lose their neurons, which is absolutely required in order to prevent the onset of the disease.

Why have treatments for neurodegenerative diseases such as Alzheimer's proven so elusive?
The field has suffered from not having the right diagnostics tools. However, now we are in a situation where for the first time we may actually be able to visualize the primary disease pathology in the brain of a Parkinson's patient. I think we have a major breakthrough. Over the last 18 months or so, blood biomarkers became available. Oskar Hanssen is certainly leading this, as he has shown that phospho-tau 217 is the number one predictive factor for getting the disease.
We are reaching precision medicine in the neuro space. Precision medicine is not based on DNA, as it is for cancer, but on the expression of misfolded proteins in the brain. We can look in the brain and dictate if you need the alpha synuclein- or tau-targeted therapy. This is precision medicine, which of course means specificity. It means safety, because you do not treat for something that you do not have, and it is cost effective because you do not treat something which costs a lot of money and does not really help you. I think we are reaching the stage now where brain diseases become reachable because we can finally look into the brain. ■

Emer Leahy

President & CEO
PSYCHOGENICS

Can you provide an overview of PsychoGenics?
PsychoGenics' mission is to transform CNS drug discovery and deliver treatment for patients suffering from severely disabling neuropsychiatric conditions. We employ our proprietary, high throughput, AI-driven phenotypic discovery platforms, which we use in combination with our broad pre-clinical discovery capabilities and mouse disease models.

Can you describe your AI-driven platforms?
PsychoGenics recognized that the target-driven approach to neuropsychiatric drug discovery had serious flaws. Instead, we pioneered a phenotypic approach that captures hundreds-of-thousands of behavioral and physiological data points from mice and employs machine learning to predict therapeutic applications for novel compounds. Not only has this target-agnostic approach delivered novel first-in-class clinical compounds, such as SEP-363856, with improved efficacy and side effect profiles for unmet neuropsychiatric needs, but it has also proven to be highly efficient delivering clinical candidates ready for preclinical development faster and requiring only a fraction of new analogs than target-driven approaches. SEP-363856 has shown significant and clinically meaningful improvement in multiple symptoms of schizophrenia with a side effect profile similar to placebo. SEP-363856, now in Phase 3, has received Breakthrough Therapy Designation.

What has the influx of capital into neuropsychiatric drug discovery meant for PsychoGenics' growth?
Neuropsychiatric drug discovery has seen more money flow into it in 2020 than ever before and almost double 2019 both in terms of institutional investment and partnering. This influx of capital is best reflected in our service business which grew significantly in 2020 as a result of many newly formed, venture backed companies requesting our services. We are also seeing more opportunities for partnerships, driven in part by the clinical success of SEP-363856 in schizophrenia, which validates our AI-driven discovery platforms. ■

Eddie Martucci

Co-Founder & CEO
AKILI INTERACTIVE

What are the origins of Akili?
Akili Interactive was founded in 2011. We are combining scientific and clinical rigor with the ingenuity of the tech and entertainment industries to challenge the status quo of medicine. We have pioneered digital treatments and care solutions to help people affected by cognitive impairments – treatments delivered through captivating action video game experiences that change the way the world thinks of medicine.
In 2020, our first commercial product, EndeavorRx, became the first FDA-cleared treatment delivered through a video game. EndeavorRx is indicated to improve attention function as measured by computer-based testing in children ages 8-12 with primarily inattentive or combined-type ADHD. EndeavorRx presented an entirely new way to treat disease, where the treatment is only possible through a digital intervention – digital therapeutics 2.0.
EndeavorRx should be considered for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs.

How does the gaming experience differ from traditional video games?
Unlike an action video game, there is no way to "win" EndeavorRx. The algorithm continues to challenge the child at a specific and consistent level of difficulty. The multitasking rules get more complex as the game progresses. As long as the child is playing consistently and trying his/her best, the child is engaging with the treatment as intended.

How can Akili's technology be applied more broadly?
We've studied our technology across 12 different indications and it serves as the foundation of a broad pipeline of programs to treat cognitive deficiency and improve symptoms associated with medical conditions across neurology and psychiatry, including ADHD, major depressive disorder (MDD), multiple sclerosis (MS), autism spectrum disorder (ASD) and various inflammatory diseases. ■

CONTRACT MANUFACTURING AND GENERICS

"Companies continue to increase outsourcing in both discovery and development. A 'nice to have', outsourcing strategy has become a 'must have' for most companies."

- Manni Kantipudi,
CEO,
Aragen Life Sciences

Image courtesy of Quotient Sciences

Timothy J. Miller,

President & CEO
FORGE BIOLOGICS

Can you provide an overview of Forge Biologics?
Forge is a hybrid gene therapy company. We manufacture AAV gene therapies for clients focused on developing novel treatment approaches in our state-of-the-art, 175,000 ft2 cGMP facility, dedicated to AAV viral vector production. We offer end-to-end development capabilities, including process development, analytical development and research grade manufacturing to accelerate gene therapy programs from preclinical stage through clinical trials. We also have a small pipeline of novel gene therapy programs, including a first of its kind treatment for patients with Krabbe disease.

Has gene therapy finally matured enough to meet its promise?
2019 and 2020 saw huge inflection points in the number of gene therapies that entered clinical trials. What we are seeing is a reflection of the power of genetic medicine, where the technology has demonstrated clinical promise, as well as safety. Now it is up to the manufacturing to catch up.

How much of a bottleneck does manufacturing represent to the growth of these technologies as commercial products?
It is a huge bottleneck – there are not that many gene therapy manufacturers that can scale up a gene therapy program beyond perhaps 50 liters of growth.

Can you outline the progress made on FBX-101 to date?
Our first of its kind FBX-101 program is a systemically delivered AAV designed to provide a functioning copy of the gene malfunctioning in patients with Krabbe disease. Preclinical data demonstrated that FBX-101 treated Krabbe mice or dogs significantly improved survival and corrected neuromuscular function. We have received FDA notification that the data supported the initiation of our clinical trial and are eager to help address this unmet patient need. Patients with infantile Krabbe disease do not often reach the age of three, and gene therapy offers a promising approach to treat the underlying central and peripheral nervous system manifestations. ■

Contract Services

SOLVING THE THERAPEUTIC DROUGHT

Similar to NFL long snappers, typically contract manufacturers are not the center of media coverage unless something has gone terribly awry. Arch Venture Partners' co-founder Keith Crandell referred to manufacturing being historically the "weak cousin" in the pharma industry constellation. However, that increasingly is no longer the case.
The critical nature of the work CDMOs perform was thrust into the national spotlight as manufacturing was relied upon to deliver one of the most critical and complex vaccine distribution efforts in history. Gil Roth, president of the Pharma & Biopharma Outsourcing Association (PBOA), an industry advocacy group explained: "Because of the pandemic the CDMO sector has never had a higher profile than it does now. The general public is starting to understand that just because it says [Drug Company X] on the label, that does not mean that is who made the vaccine or therapeutic."
This heightened awareness of the general public has also meant that Congress and the FDA have been willing to take a deeper look into understanding how the sector works and the essential role manufacturers play in bringing therapies in development to reality.
It helped that companies in the manufacturing space stepped up and delivered despite enormous complications around social distancing, worker safety and supply chain unpredictability. These businesses were deemed essential from the get-go, and many never shut down. Jeff Reingold, COO of Contract Pharmacal Corp, based in Hauppauge NY, offered a story that epitomized the can-do nature of the industry. "When you are a manufacturer you need the machines running, so the safety piece was very stressful. At one point, we had four lunch breaks for one eight hour shift because we were limiting how many people could be in the cafeteria."
A challenging human resources environment meant that CPC, along with many others in the space, could not manufacture at full capacity, thus had to make decisions around what to produce. "We could not make everything, but we wanted to make sure that what we could make fit within our customers prioritization. Adding to this complexity was the fact that bottles and caps were not available. Lead times on materials were longer and it pushed us to think differently and to focus on what we have, what we are capable to produce, while also considering the timing on future productions based on expectations from our vendors," said Reingold.

Speeding to market

For early-stage companies, timelines matter. Funding is tied to timelines and milestones being met. Companies operate within a finite window to achieve proof of concept or progress through a clinical trial, so being marred by delays in the manufacturing process can mean failure. At the later stage, manufacturing holdups also have harsh consequences for the economics of a product, and in cases such as vaccine development, it can mean many additional lives lost. This was evinced by the FDA's actions asking JNJ to scrap up to 15 million Covid-19 vaccine doses and temporarily halt production over an er-

ror made at an Emergent BioSolution's manufacturing site. This means that other vaccine makers such as Moderna and Pfizer will continue to handle the bulk of vaccine production.

CordenPharma represents a leg of the mRNA supply chain, as it was awarded the contract to supply critical lipid excipients for Moderna's Covid vaccine formulation. When asked about the factors that enabled CordenPharma to move in such a fast manner to bring this product to market, Michael Quirmbach, the company's CEO and president, responded: "The key is all about having critical size, great teams in place and quickly making the right decisions. When we were approached by Moderna we immediately understood the complexity. We put a global team together, relying on various competencies, and we used our global facility network to scale up rapidly. Initially, work started in Switzerland and soon after, we involved other sites as part of our network."

> *You might only use the injectable equipment if you are producing a particular drug one or two days a month, which would not make sense to invest in if you were a pharma company. Whereas if you are a CMO it would make great sense because you can run many different products on that same line. The cost and complexity of equipment has gone up dramatically while the run sizes have gone down. Consequently, it plays into the CMO strategy of investing in biologics capacity.*
>
> ***- Brad Payne, COO, PCI Pharma Services***

Quotient Sciences, which sees itself as a drug development and manufacturing accelerator supporting pharmaceutical and biotech companies, is another company extraordinarily focused on speed to market. Its' Translational Pharmaceutics platform integrates disciplines around drug product manufacturing and clinical testing that are traditionally found in different silos in the outsourcing industry. By integrating these activities and very closely aligning workflows around manufacturing and clinical testing, Quotient demonstrated that at least 12 months could be saved on the drug development timeline. "The traditional outsourcing paradigm is very siloed, meaning if customers want to do drug product manufacturing, drug substance manufacturing and clinical testing, they would need to go to a separate CDMO or CRO for each of these services," Quotient Sciences' CEO Mark Egerton explained. "Quotient's approach offers a single supply chain managed by a single project team, in which we are able to provide all of these services to our customers all at one organization, which in turn makes a contribution to their time savings or efficiency saving."

Software assists timelines

When it comes to manufacturing timelines, validation is another area that can be burdensome. The FDA defines vali-

Manni Kantipudi & Ramesh Subramanian

MK: CEO
RS: CCO
ARAGEN LIFE SCIENCES

MK

RS

> **There is little interest in setting up new labs with large footprints that cost both time and money: the focus is on speed while levering service providers that have both competence and scale.**

How is GVK BIO's name change to Aragen Life Sciences reflective of the company's evolution?

We are celebrating our 20-year anniversary in 2021, and the management team felt that time was right for a rebrand to best represent the company and its position today. From our modest beginnings, as a chemistry service provider with one site, we have now grown to 3,000 employees and seven global sites, including two in North America and five in India. We have added significantly to our small molecule capabilities and are now a preferred partner in offering discovery chemistry and biology, chemical development and manufacturing solutions, while rapidly expanding our relationships in formulation and analytical development solutions. In large biologics, we are the Partner of Choice for customers working with hard to express proteins and are a leading provider of Cell Line Development and Bio-Production services.

We assist customers in over 10 IND filings each year and have executed over 75 Chemical Development programs over the past year. We have partnered with our customers in launching five NCEs thus far, expect to launch an additional four in the next 12 months, and three of our Cell Lines have been taken into commercialization.

What macro trends are driving growth in Aragen's business?

We are seeing four major trends. First, there is more capital going into the pharmaceutical and biopharmaceutical R&D, with several startups getting well capitalized. 2020 was a banner year for venture funding with over US $23 billion invested (vs 2019: ~US$17 billion). In addition, large pharma companies also increased their R&D budgets, so the growth there has been positive too.

The second trend is that most of these companies continue to increase outsourcing in both discovery and development. From a 'nice to have', an outsourcing strategy has become a 'must have' for most companies. There is little interest in setting up new labs with large footprints that cost both time and money: the focus is on speed while levering service providers that have both competence and scale.

The third trend we see is the balancing of the supply chain. Firms that had a supply chain that was skewed towards China are looking to diversify and de-risk their sourcing strategy, with Western and Indian companies both becoming the net beneficiaries.

Fourth, since Covid-19 pandemic, we have seen an interest to work with service providers that took the right precautions to protect employees - via working shifts, social distancing protocols, implementation of system and processes that ensure staff health- faring better than firms that did not.

In summary, through the pandemic and due to the macro drivers listed above, Aragen had its best year ever.

In what areas is Aragen's expansion most focused?

We are adding significantly to our capacity in small molecule discovery with expansions in India. In development, we recently invested in doubling our API capacity and are well positioned to meet our customers' needs for the near future. With the increasing interest in integrated development, we are expanding our drug product footprint by investments into drug product manufacturing. We should be ready to support our customers' clinical needs by the end of the year. Our biologics business has grown significantly post acquisition with our pharma and biotech partners requesting manufacturing to go along with our industry leading Cell Line Development (CLD) offering. We recently approved this investment in North America and expect to have a state-of-the-art facility for Cell Culture Manufacturing in about 24 months.

Aragen has doubled the size of its cell line business over the past two years. How will the addition of GMP manufacturing complement this growth?

Aragen-US is known globally for its capabilities in CLD, the subsequent stage of which is GMP manufacturing. We want to forward integrate CLD into the manufacturing process as most of our biotech customers like to work with one CRO/CDMO to get their cell line expressed and generate clinical material at the shortest time frame and advance to test safety and efficacy in clinical trials. These customers prefer working with one partner over tech transferring a CLD process to a different partner. ■

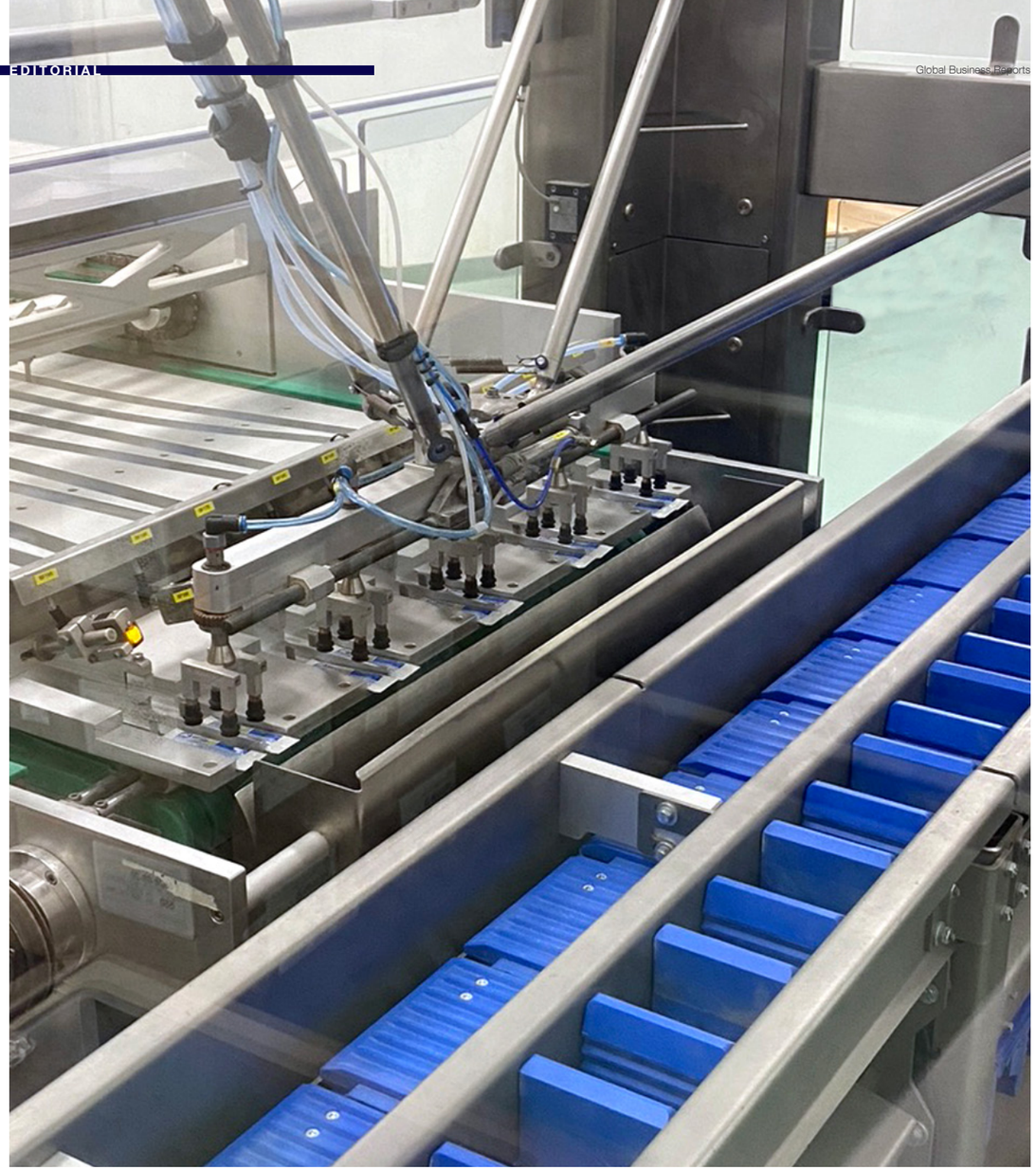


Image courtesy of Contract Pharmacal Corp

dation as "a process that is required to establish documented evidence to assure that a specific system, equipment, computer system, or process will consistently meet the requirements of its intended use." All organizations need to validate their systems, computers, equipment, and processes that have GMP impact.

This has significant bearing on companies involved in pharmaceutical manufacturing where typically these processes were done manually in addition to being paper based. Usually, with any validation lifecycle process, there are nine different lifecycle stages, and now contract manufacturers are outsourcing their validation work by purchasing software from companies like ValGenesis, who manage each of the nine distinct validation lifecycle stages as a module and connect the dots that flow data from system assessment and author requirements up to the retirement stage. Siva Samy, CEO and chief product strategist at ValGenesis, explained: "ValGenesis makes the end-to-end validation lifecycle process 100% digital, reducing validation cycle time by over 50% and thus, helping life science companies release their products to market more quickly… Most of our clients are involved in manufacturing lifesaving drugs. Many of their production lines were identified as essential to keep products getting to market on time during the pandemic. With the help of the ValGenesis platform, our clients can now manage the validation process remotely or with limited onsite resources, without any disruption to their supply chain". ■

Jeff Reingold

COO
CONTRACT PHARMACAL CORP

2021 marks 50 years for Contract Pharmacal Corp (CPC). What are the key components of building a company that has endured the test of time?
The CPC story exemplifies the American dream. John and Harriet Wolf started this business 50 years ago in a garage in Connecticut. When I began my career at CPC 13 years ago, we were approximately 200 people in two buildings. Today we are 1,400 people across 11 buildings. Since the day we opened our doors in 1971, we have been driven by quality, visionary thinking, and a strong foundation of values. Currently owned and operated by the second generation, Mark and Matt Wolf have been defining the state of excellence that are critical to the goals of exceeding our customers expectations. Production has more than quadrupled during my time at CPC and we are on track to beat our record number from last year.

How has CPC been able to continue its operations while also providing a safe workplace throughout Covid?
Our business was deemed essential from the get-go so we never shut down. We quickly put many precautions in place such as mask wearing, temperature checking, social distancing, installation dividers where we could, and allowed certain departments to work from home. A lot of our operations require people to be here. When you are a manufacturer you need the machines running, so ensuring safety was very stressful. As a result, our production capabilities were impacted. Adding to this complexity was the fact that bottles and caps were not available. Therefore, lead times on materials were longer and it pushed us to think differently and to focus on what we have, what we are capable to produce, while also considering the timing on future productions based on expectations from our vendors.

Did Covid bring about a spike in demand for certain CPC products?
There was a lot of enthusiasm around the "Covid cocktail" consisting of vitamin C, vitamin D, and zinc. We brought in a lot of new equipment to support capacity growth.

What has been the impetus for CPC's continued acquisition of manufacturing facility space?
We strive to do a good job of assessing our business needs and our capacity utilization today, six months from now, and where we see ourselves in three, five and 10 years. We know certain business avenues that we are going after, and we know how to set up the bodies to support that. The big one for us is space. As we take on new business, we need more of everything. It is not as simple as wanting to make more tablets and going and buying a tablet press. We also have to feed that tablet press more raw materials, which means my incoming warehouse has to receive more raw materials. My incoming raw material testing laboratory and quality control lab has to release more materials and my finished goods lab has to release more materials on the backend. As a result, we have to store more finished goods. The business has to be able to absorb the growth depending on what we are looking to do. This additional space now allows CPC to grow certain areas of our operations that we are looking to streamline and find efficiencies.

> We know certain business avenues that we are going after, and we know how to set up the bodies to support that. The big one for us is space. As we take on new business, we need more of everything.

What are the most important aspects of CPC's growth strategy moving forward?
We see many opportunities to grow organically with our existing partners. In addition, we are excited about opportunities in additional retail business and the prescription generic space, as the Florida Pharmaceutical Products (FPP) acquisition is continuing to blossom. There are many products we are working on in the pipeline that will support our generic operation, which is a promising area for CPC.
In addition, we are looking closely at novel technologies and different packaging solutions along with different dosage forms. Having the opportunity to grow the business in a lot of different areas is what we are looking for. This is all while continuing to focus on our core expertise which is solid dose manufacturing and packaging. On the back of our success throughout 2020, more companies now look to CPC as a company that can deliver despite the chaos of the external world. ■

Mark Egerton

CEO
QUOTIENT SCIENCES

Can you provide an introduction to Quotient Sciences?
Quotient Sciences is a drug development and manufacturing accelerator that supports pharmaceutical and biotech companies with services spanning the entire development pathway from candidate selection to commercial launch. With operating facilities in both the UK and US, we deliver uniquely integrated programs or a range of tailored services that allow our customers to accelerate their development timelines and get life-changing medicines to patients faster. Approximately 12 years ago, we created a new innovative platform called Translational Pharmaceutics™ which integrates disciplines around drug product manufacturing and clinical testing that are traditionally found in different silos in the outsourcing industry. By integrating these activities and very closely aligning workflows around manufacturing and clinical testing, we demonstrated that we are able to save at least 12 months on the drug development timeline. This translates into helping customers accelerate new medicine development, save time, money and give a better chance of a good outcome from the development program. If you take those 12 months and translate that into economic value to a customer, it comes out at around US$200 million for every molecule that makes it to market. The financial benefits were quantified in a 2020 publication written by the Tufts Center for the Study of Drug Development.

What are some of the ways in which Quotient helps clients conserve cash?
The integrated approach that Quotient has developed allows for a rapid "make-test" cycle that is under a single flexible clinical protocol. This enables you to manufacture a formulation and dose it in a clinical study to see the impact of that formulation and how it works to deliver the active substance. Then you can modify the formulation composition to improve the delivery by using real-time clinical data. This can be done in 14-day test cycles. Therefore, as the clinical program is developing, we can iteratively use clinical data to deliver an optimal drug product composition. We can then seamlessly take that product all the way through to proof-of-concept and on to commercial manufacture if the molecule is successful.

What was the impetus for Quotient's acquisition of Arcinova?
What interested us in Arcinova is their expertise in early-stage drug substance and bioanalysis work, accompanied by their isotope labelling capabilities that are complementary to our existing 14C ADME services. With regard to drug substance, we see a great opportunity in integrating drug substance services into our platform. There are many occasions where we cannot start our program on the planned timeline because the customer is not able to deliver their drug substance to us. Therefore, we feel it is a great opportunity to integrate drug substance, drug product and clinical testing capabilities. Both Arcinova and Quotient both are able to work on the molecules early, just as they are coming out of discovery.

> By integrating these activities and very closely aligning workflows around manufacturing and clinical testing, we demonstrated that we are able to save at least 12 months on the drug development timeline.

What is Quotient's approach to hiring and retaining top talent?
Human talent is the fundamental ingredient for any service organization like ours. As the industry pipeline has expanded, the funding has expanded, the number of molecules expanded, and, as a result, there is more work to do. Talent management and talent acquisition have become crucial aspects of business development. From my perspective, there are some simple ground rules for how we develop the business. First, we must be an exciting place to work, because talented people want to work in places where they feel they can make a difference, not just in how they do their job, but in what the company is trying to contribute into the general initiative around healthcare and wellbeing. We have always strived to have this differentiated position and that has served us well in terms of attracting talent. Secondly, career growth and personal development is essential. When talent comes to Quotient, you must give people the space to develop and spread their wings and achieve their potential, because if they achieve their potential, then that is only going to benefit the business. Employees put their trust in companies to help their careers, and if companies cannot support them to develop, then employees will go somewhere else. ■

Jonny Ohlson & Tommy Duncan Koppen

JO: Executive Chairman
TD: CBO
TOUCHLIGHT GENETICS LTD.

JO

TD

What is the strategy behind Touchlights' hybrid business model?
Touchlight is focused on enabling the industry for genetic medicine, whether it is production of viral vectors for gene therapy or production of nucleic acid medicines, such as mRNA or DNA vaccines. The real thrust of our model is behind getting broad adoption of our technology as a contract manufacturing company, but there are all of these new industries that turn up, such as base editing or certain genome editing applications. We believe it is imperative to invest further in those future applications of the dbDNA platform in order to generate the full value of what it can do.

How does Touchlights' Doggybone DNA technology overcome the inherent issues of plasmid?
The difference between the Doggybone platform and the plasmid DNA production platforms is that we eliminate cells, so we are an acellular or synthetic process for making DNA. We do this by utilizing enzymes to amplify our DNA material. What can be done in a bioreactor at 300 liters for fermentation to make plasmid, we can do in a couple of liters on a benchtop. That alters the cost structure of how you produce DNA. We are amplifying DNA, where we use enzymes and nucleotides and have them amplified together and purified, taking the DNA away from the enzyme.

How is the program with Cancer Research UK in therapeutic DNA vaccines paving the way for other therapeutic players to use Touchlight's platform?
It means that we can blaze our own path through the regulatory processes to be the first people to control the clinical dosing of dbDNA as a direct therapeutic. That has huge benefits in terms of a halo effect on our platform because it answers a huge number of questions that a client might have about the validity, comparability, and the tox package of the dbDNA platform. ■

Jeremiah Marsden

President
CASCADE CHEMISTRY

How has Cascade Chemistry evolved?
Performing R&D for pharmaceutical companies still remains our core, but our focus now is on process development, scale up of API's and getting from the R&D stage into manufacturing for GMP.

What are the key problems Cascade helps clients solve?
Typically, there are two primary problems customers come to us with. First, when their API lead compounds are still in discovery they may have made a few grams of it, but now they need to figure out better chemistry, how to scale it up, and develop a process suitable for manufacturing at scale in a GMP environment.
Secondly, clients may have had another manufacturer running a Phase I GMP batch but the chemistry was not well worked out. They come to us to fix the process.

What opportunities does Cascade see to grow its API contract business?
Our growth in the last few years has been very organic and client driven, as our clients are always asking us for larger scale and greater capacity. Client need got us into GMP manufacturing, and client need is driving us toward commercial API manufacturing. There are also many opportunities for clients getting new drugs from discovery into early clinical trials.

What are your views on running a CDMO out of Oregon?
The University of Oregon is here in Eugene, Oregon State is a 40 minute drive away and both have great chemistry programs in organic synthesis. University of Oregon has its new Knight Campus where its focus is on translating professors' research into new companies, and also training students for industrial positions in the pharma industry. We are able hire many quality recruits from the universities. There are also other manufacturing sites in Oregon that we have been able to tap into including other CDMOs and larger scale manufacturers. ■

CDMO M&A and Investment

Prior to the arrival of Covid, the CDMO space in the US was fertile. Multiples for CDMOs had risen considerably over historical levels, reflecting the extreme need for reliable companies to outsource to. Investment and consolidation followed, reshaping the nature of the industry and the offerings of many of its companies.

One aspect was that mega deals were done to acquire specific technological capabilities. Catalent's acquisition Paragon Bioservices for US$1.2 billion, and Thermo Fisher Scientific's acquisition of Brammer Bio for US$1.7 billion are examples of this strategy at work, as both wanted access to the cell and gene space without having to build from nothing.

While much attention has been paid to acquiring capabilities in the cell and gene and large molecule biologics area, small molecules still play a prominent role in looking at FDA approvals as they more frequently obtain orphan designation and fast-track status.

Dipharma Francis has been building on its' specialization in the small molecule custom synthesis market in recent years. The company acquired Kalexsyn, a CRO based in Kalamazoo, Michigan in 2018, and rapidly expanded on their capabilities. Since the acquisition, Dipharma has built a brand-new state-of-the-art GMP suite, which has been fully operational since early 2020. On the back of this progress, the company modified its business model creating two distinct business units: one fully dedicated to APIs for generics, and another exclusively focused on CDMO activities. "This strategic move was intended to expand our operational platform in North America. We have since been integrating our Kalamazoo facilities and capabilities into our project development network in Italy in order to optimize our company's value proposition. As a result, all our sites across different locations work closely together," affirmed Jorge Nogueira, CEO of Dipharma Francis.

Supply chain planning has been extremely tough, as lockdowns across the globe complicated access to supplies. Opportunities came on various occasions but fulfilling those opportunities was challenging.

- Swapnil Shah, Managing Director, Espee Group

There has been an increase in activity and innovation in the oral drug delivery space, thus several important deals have been made to enhance competitive positioning. Notably, in 2017, Lonza closed its acquisition of Capsugel for US$5.5 billion. Four years later, the legacy Capsugel business (now called Capsules, Health and Ingredients (CHI)) has been successfully integrated into Lonza's broader business, and the company is now capable of providing CDMO services to help customers develop the API while its CHI unit assists in the development of the right delivery solution. "We are finding that delivery dosage is a critical component of the overall API, and the delivery form you choose impacts the efficacy of either the drug or health supplement. For example, if you are taking a probiotic, the location and timing of release become very critical. We work with our customers to find the right polymers so that the ingredients do not prematurely release in the gut where the probiotic would be killed. We develop them to release at the right location and in a particular timing profile. Some customers might want immediate release, others might prefer a designed release," noted Ramin Cyrus, vice president marketing at Lonza Capsules and Health Ingredients.

On the heels of this deal, in 2020 Frazier Healthcare Partners teamed up with Thomas H Lee Partners to acquire Adare Pharma Solutions, a CDMO specializing in oral solid dose products with a set of proprietary manufacturing technologies.

In its pursuit of becoming an end-to-end CDMO partner to pharmaceutical companies, Adare has remained active, acquiring Orbis Biosciences in May of 2020. According to Adare CEO Vivek Sharma: "Through our acquisition of Orbis, we have expanded the solutions we can offer our customers to include oral liquid for extended release and taste masked formulations and, most exciting, injectable forms."

With Adare's renewed focus on pharma service and technological capabilities, it has been adding more capabilities in the solubility enhancement area, including its Optimμm technology from the Orbis acquisition. Sharma added: "We can help patients take less drug due to an optimized solubility profile or provide them the flexibility to take a drug with or without food. With our customized solutions we can help patients ingest a prescribed drug, which improves compliance and has corresponding health benefits."

A Strong Start in 2021

The string of investments has continued thus far into 2021, with Signet Healthcare Partners investing in Ascendia Pharmaceuticals, a company known for its expertise in providing custom sterile and non-sterile enabling formulations and analytical methods for new chemical entities, complex dosage forms, and 505(B)(2) product development. This investment will enable further innovation to meet the companies growing production needs for early and late phases of product development. "Ascendia has been bootstrapping for the past nine years with a friends and family round. Our growth strategy includes a strategic partner and we are pleased to have just announced that we received a growth PE investment from the esteemed Signet Healthcare Partners to grow and expand our people, capabilities and facilities to meet and exceed customer expectations from early to late state development," affirmed Robert Bloder, Ascendia's chief business officer.

To illustrate the impact Ascendia can have on a client Bloder mentioned that in the past year, it has worked with an oncology startup, moving very quickly with a product that was working well on cancer as a target. Unfortunately, it required 50 to 60 pills per day after the patients had failed three rounds of chemotherapy. Bloder expounded: "The company was about to lose their funding because it was not a viable option for these patients despite the dire straits they were in. Ascendia was able to improve the bioavailability and decrease the dose to 10 to 12 pills per dosing, which has provided for the project to continue with funding."

Blow-Fill-Seal

The Blow-Fill-Seal (BFS) space has also seen action from investors over the past year. To start 2021, SK Capital Partners closed an acquisition of Catalent Pharma Solutions' Blow-Fill-Seal Sterile CDMO business and changed its name to Woodstock Sterile Solutions. Alan Petro, CEO of New Vision Pharmaceuticals, a company with deep expertise working with Blow-Fill-Seal technology, believes there are a number of reasons why the technology is being adopted more widely today. "Drugs are becoming more potent and doses are getting smaller, therefore, the doses must be more precise. At the same time, the global population is getting older and drug packaging must become more patient-centric and easier to use. BFS packaging is ideally suited to meet these needs," he says.

This need was particularly important as Covid lockdowns limited access to traditional points of medical care. One of the unique aspects of Blow-Fill-Seal is the single use doses that in many cases are sterile. This helps with issues of overdosing in pediatric cases.

The technology also has concomitant advantages of being significantly lighter in weight than glass containers, unbreakable in transit and it is not subject to spoiling. These factors result in lower shipping costs and fewer potential end-to-end quality concerns. ■

Jorge Nogueira

CEO
DIPHARMA FRANCIS

How has Dipharma evolved from its origins to today?
Dipharma was founded in 1949 by Mario Biazzi, who created an innovative concept to manufacture nitroglycerin using a continuous process. His major concern back then was safety, because nitroglycerin was produced with a batch process, often resulting in severe accidents. He came up with the idea of a reliable and safe continuous process, and for many years that was our main product. In the sixties we found ourselves getting requests for nitroglycerin in medical applications, and by the seventies we had become a major player in the generic API market. We also received our first FDA GMP audit, which means we have five decades of proven experience in this field. From then on, our business model centered around building a successful pipeline of new generic APIs and select contract manufacturing services for pharmaceutical companies worldwide.
About three and a half years ago we began considering expanding our CDMO business because we saw an attractive potential for our broad scope of capabilities and resources. In 2020, we modified our business model by creating two distinct business units. One is fully dedicated to APIs for generics, the other is exclusively focused on CDMO activities. In anticipation of this move, in 2018 we acquired Kalexsyn, a CRO that is based in Michigan. It offered well-established CRO services which we rapidly expanded, including a brand-new state-of-the-art GMP suite which has been fully operational since early 2020.

How does the Kalexsyn acquisition fit with Dipharma's broader global strategy?
Our investment in Kalexsyn was the starting point to reinforce our global presence through a stronger platform in the U.S. A key element for us is to anticipate where the market is going and position our business accordingly. The ability to have marketing activities and eventually manufacturing facilities in different places around the world always brings a more realistic perspective of how the market is evolving. This is essential to ensure the proper positioning for our company when it comes to technological trends, resource allocation and capital investment.

How does Dipharma strategize where it locates its facilities?
For us, overall competitiveness is a primary focus. This means not only the process technology involving a given product, but also whether we focus on reaching best practices on everything else revolving around that product, like process safety, quality, and many others seeking overall operational excellence. All these factors are critical to provide the flexibility and the sustainable reliability our customers require.
Perhaps sometimes we jump to the conclusion that it is better for us to manufacture in one place over another. I believe the current pandemic has taught us about the inherent risk of over-dependence on certain regions under the assumption of lower costs only, until discovering that the whole value proposition was not properly evaluated.
Our most recent capital investment, for instance, involved the duplication of our pilot plant at our Mereto facility in Italy.

> In 2020, we modified our business model by creating two distinct business units. One is fully dedicated to APIs for generics, the other is exclusively focused on CDMO activities.

How are advances in technology influencing Dipharma's business?
Dipharma was born from an innovative idea and technology has been our backbone ever since.
We approach technology from different fronts to maximize its critical mass. We have, for instance, been investing considerably in continuous processing which will revolutionize production practices in the foreseeable future. We have the advantage of counting within our group the leading company in reaction technology (Biazzi SA), and we have, therefore, been co-developing new projects to support continuous production that we will implement in the future.
We are also building additional R&D capabilities since we want to be able to propose creative ideas to substantiate our customers' projects and ambitions. But our focus is not solely about yields, and it is not down to the chemistry alone. If you focus only on the chemistry, you might find some success, but the full picture tells you that customers equally value flexibility to adjust to their needs and timelines along with spotless reliability. That is why those factors are at the top of our priority list. ■

Alan Petro

CEO
NEW VISION PHARMACEUTICALS

Can you provide an overview of New Vision Pharmaceuticals?
New Vision Pharmaceuticals is focused on providing exact dose Blow-Fill-Seal technology for a wide variety of formulations and products. We provide confidence and quality to the Rx, OTC, diagnostic reagent, cosmetic and dietary supplement markets. We help clients make their product through reformulation, more economical production methods, better packaging and improved customer presentation.

What are the underlying trends diving the adoption of Blow-Fill-Seal technology?
There are a number of reasons why Blow-Fill-Seal technology is being adopted more widely. Drugs are becoming more potent and doses are getting smaller. Therefore, the doses must be more precise. At the same time, the global population is getting older and drug packaging must become more patient-centric and easier to use. Especially with seniors, the packaging must be easy to use to allow treatment in the home. Blow-Fill-Seal packaging is ideally suited to meet these needs. This need has been especially important as we have transitioned through a variety of lockdowns that limit access to the traditional points of medical care.
Blow-Fill-Seal technology is recognized by USP 1116 as an advanced aseptic process that allows for superior microbiological control, precise filling accuracy, exceptional process and product reliability, the capacity to apply inert cover gases and adapts to a wide variety of formulations. It has concomitant advantages of being significantly lighter in weight than glass containers, unbreakable in transit and not subject to spoiling. These factors result in lower shipping costs and fewer potential end-to-end quality concerns. It has the additional benefit of being counterfeit resistant which enhances public confidence and overall safety.
While Blow-Fill-Seal technology has been long been established in Europe, its introduction in the US and Asia is accelerating. Even though the production equipment is costly to purchase and maintain, it provides excellent economy of scale through its high production rate, exquisite quality and low labor requirements. It enables highly automated, precision manufacturing which delivers quality products in a very cost effective manner.

> We believe that there are several drivers for increased application and acceptance of Blow-Fill-Seal technology.

How does blow, fill, seal boost adherence?
One of the unique aspects of Blow-Fill-Seal is the single use doses that in many cases are sterile. This enables us to reduce the issues of overdosing in pediatric cases.

What are the most important areas of growth and investment for New Vision?
Today we are adding high volume Blow-Fill-Seal capacity to meet customer needs. As we speak, another machine is being prepared for shipment from Germany and will be fully operational later this year. This will bring to six the number of BFS machines in house. We anticipate making investments in the support systems, including enhancing track and trace to support evolving regulatory needs.
We are also focusing on developing an empowered and highly flexible organization that can bring client ideas to fruition more quickly. This means that concepts can move rapidly into phase 2 production and later easily transition to phase 3 and ultimately commercial manufacturing. We believe that there are several drivers for increased application and acceptance of Blow-Fill-Seal technology. These trends suggest that New Vision Pharmaceuticals is well positioned for market growth.

What are the primary goals of the company moving forward?
Our primary goals are to fully utilize the significant investment that we have made over the last several years in the facility and staff. We have an excellent team who have demonstrated the ability to give clients the quality and schedule reliability they need to deliver innovative products. In the coming years we want to do the same, but with quicker project schedules and the ability to assist if and when the next public health issue presents itself. Through our capabilities, we can quickly bring generics to market, reduce our country's dependence on offshore drug manufacturing and deliver products with enhanced anti-counterfeiting features. ■

Ramin Cyrus

Vice President Marketing
LONZA CAPSULES AND HEALTH INGREDIENTS

How does Capsugel fit within Lonza's broader corporate structure?
If you look at Lonza historically, we provide CDMO services to help pharmaceutical companies get their products to market. Our CDMO business helps customers develop the API, while Capsugel assists in the development of the right delivery solution.

Can you point to a case that illustrates the services CHI provides?
We are finding that delivery dosage is a critical component of the overall API. One of the areas we are heavily focused on is multi-dosage ingredient delivery, where you may have two separate ingredients, and they are physically separated in the capsule because you want them to release at different times or in conjunction with one another.

What trends are driving Lonza's investment in building out its manufacturing network?
We have seen a trend towards supplementation. More people are focused on their health. As a result, we saw a healthy surge in demand for capsules, but also, we have an ingredient side of the business where we make sports nutrition and joint health products and we saw an overall jump in demand there. This demand was so high that we had to accelerate our capacity expansion plans. We received about 85 million CHF in capital investment to expand our global manufacturing network to keep up with demand. We saw this demand coming a long time ago, but Covid compressed timelines.

What are the fastest areas of growth within CHI's business?
The highest growth is in the nutraceutical market. We also see a shift in demand to clean label products or clean label capsules. The trend is more towards vegetable-based products.

How does Lonza strategize around where to locate its facilities?
We need to be close to our customers, so as our pharmaceutical and nutraceutical customers move their manufacturing bases, we have to adjust to where they are for logistical and regulatory reasons. ■

Peter DeYoung

CEO
PIRAMAL GLOBAL PHARMA

Can you provide an overview of the key developments for Piramal Pharma Solutions (PPS) in 2020?
In 2020, Piramal Pharma Solutions (PPS) embarked upon an increased focus on patient centricity as our core ideology. When the Covid-19 pandemic broke out, our initial focus was to ensure employee safety at our factories. We focused on getting medicines to patients so that there would be no shortage of critical medicines that help reduce the burden of disease. Largely, we had no major interruptions in supply throughout our network and there were no major delays in getting medicines to customers.
Before the Covid-19 pandemic, PPS had very exciting ambitions to grow, but did not have enough capital to achieve all of our growth objectives. We embarked on a fundraising process, ultimately selecting and securing Carlyle Group as our growth investment partner in June 2020. In return for a 20% stake in the business, Carlyle will provide PPS with the investment capital and complementary expertise to take our business to the next level. We also realized that we were missing a piece of our puzzle in terms of drug product in the US. As a result, PPS expanded the company's portfolio by acquiring a drug product facility in Pennsylvania, capable of delivering potent solid oral dosage forms as well as creams, liquids and ointments.

Which technologies do you find most promising for CDMO's in the future?
An area that has been receiving significant interest over a sustained period is potency-related manufacturing capabilities. PPS continues to invest in high potency technologies. Another area of interest is solubility-enhancing technologies.

Can you highlight some of the key growth areas for PPS?
First, our integrated product offering is a huge part of what we are selling for new projects and this area is growing exponentially. Secondly, PPS is heavily invested in getting new development programs into our overall portfolio. ■

Vivek Sharma

CEO
ADARE PHARMA SOLUTIONS

Adare's new investment partners bring industry and operational expertise to help Adare accelerate its growth as a CDMO.

What factors influenced Frazier and THL to purchase Adare?
Adare's new investment partners bring industry and operational expertise to help Adare accelerate its growth as a CDMO. Frazier Healthcare Partners, a leading healthcare-focused private equity firm, and Thomas H. Lee (THL), a premier global middle-market investor, have had much success together building business and creating value, particularly in the pharma services space. The firms saw that Adare was an asset with significant technical capability, deep customer relationships, and a strong vision to be a differentiated, technology-driven CDMO. We believe that under THL and Frazier's leadership, Adare will achieve that vision and prove itself as an end-to-end CDMO partner to pharmaceutical companies.

What is the strategic direction of Adare?
Overall, in the pharmaceutical industry, there is a growing trend toward outsourcing, and it will continue to grow into the future. Manufacturers that have strong capabilities, technologies and unique solutions to solve complex problems will be selected as partners. Adare fits into that profile. Adare's proprietary technology and capabilities make it well positioned to serve even the most complex needs in the drug development space. It has tremendous experience in bringing products to market. Our patented technologies solve the most complex problems, allowing us to develop and manufacture transformative medicines. That is what was exciting for all of us to make an investment in Adare. It has the potential to be a mainstream CDMO, which was not done by the previous ownership.

How will Adare's acquisition of Orbis Biosciences enhance the company's offering?
Our investment in Orbis provided Adare an entryway into long-acting injectables, a space the company had its eye on for a long time. Orbis offers complementary capabilities to Adare's capabilities in the oral space. Through our acquisition of Orbis, we have expanded the solutions we can offer our customers to include oral liquid for extended release and taste masked formulations and, most exciting, injectable forms.

How is Adare addressing the issue of poor insolubility in oral drug delivery?
With our Bioris technology we have been one of the pioneers in this area. In recent years we focused more on taste masking, controlled release, and orally disintegrating tablets, however with our renewed focus on pharma service and as a technology-driven CDMO, we have been adding more capabilities in the solubility enhancement area, including the Optimμm technology from the Orbis acquisition. Today, we can help patients take less drug due to an optimized solubility profile or provide them the flexibility to take a drug with or without food.

Can you provide an overview of ADARE BIOME? What do you see as the promise of the microbiome as an emerging field?
Today, Adare Biome develops solutions for Human and Animal health and nutrition. We have just hired a new leader to oversee that business and accelerate growth, with greater focus on providing solutions in the area of postbiotics. We have a huge presence in the European market, and we are now trying to expand and partner with companies in North America where we see a huge potential for growth. Overall, we think that the experience and solutions we offer can create significant value for a multitude of different companies. We are adding talent and investing capital in this business to further boost our capabilities. Our goal is to become a premium microbiome supplier.

What is your outlook on Massachusetts as a life sciences cluster looking forward?
Pharma has a huge R&D presence in the Massachusetts area, and most of it is driven by talent availability arising from the ecosystem. That is the key aspect of its attractiveness. While it has abundant opportunities, it also has challenges. It is hard to find talent in the Boston area due to the fierce competition. At the end of the day, it is all about where people are, and where they want to be. With the number of universities and resources that are out there, it will remain a very attractive place for pharma R&D. However, given some of the cost challenges, you will see other areas develop. At Adare, we see our markets (Ohio, Kansas, New Jersey) as attractive markets to recruit talent and places that people will be excited to plant roots and create meaningful lives. ■

Shaun Chilton

CEO
CLINIGEN GROUP

What is the critical problem Clinigen solves for patients and pharma companies?
Clinigen exists to facilitate access to hard to find medicines. We do that through a services and product platform that we have built over the last decade. We operate at specific time points throughout a medicine's lifecycle, from pre-approval through to post-approval to extend and expand that lifecycle by maximizing access to that medicine.
Even in the US, the biggest market in the world, at any given time there can be over 100 products that are listed on the FDA website as being in shortage of supply. This only gets worse as you go through the rest of the world. Clinigen's mission is to help manage and improve that situation.
Fundamentally what makes us different from others involved in pharma and healthcare is that we manage a market, whether it is licensed or unlicensed, so there is no barrier to being able to supply a medicine and distribute it, even if the drug has not been approved in that country.

What factors will drive Clinigen's market performance in the medium term?
Our services and products are in demand and there is significant unmet and/or underserved need in what we do. Even if we just kept pace with market growth and made no market share gains from the competition, we would still be capable of delivering decent organic growth.
Interestingly, we are extremely cash generative, and on average since inception, we have converted on average about 85% of our EBITDA into free cash.
The piece that might surprise some is our digital platform. We have been dubbed, the 'Amazon of Unlicensed Medicines', because increasingly pharmacists, physicians, and pharmaceutical companies want to interact online. We spent a couple of years focusing on that software piece, and we are rolling it out now as a suite of online services that will be localized and tailored. ■

Michael Quirmbach

CEO & President
CORDENPHARMA

CordenPharma was awarded the contract to supply critical lipid excipients for Moderna's Covid vaccine formulation. How was CordenPharma able to react so quickly?
When we were approached by Moderna we immediately understood the complexity. We put a global team together, relying on various competencies, and we used our global facility network to scale up rapidly. Initially work started in Switzerland and soon after, we involved other sites as part of our network.

How does establishing a relationship in one area with a biotech company lead to a deeper relationship over time?
In general, we have a broad service offering in excipients, API and drug product manufacturing which allows companies multiple opportunities in working with us. This goes along with the trend that as companies simplify their supply chain, they look for partners who can offer end-to-end or integrated services.

CordenPharma recently launched an investment in continuous manufacturing in France. How is this investment progressing?
The advantage of this type of continuous manufacturing is that you can run chemistry which might otherwise require much larger capital investment and infrastructure. Continuous manufacturing can therefore give the customer a real benefit when manufacturing certain complicated APIs with complex steps. It is also more environmentally friendly by reducing the amount of solvents used, or employing certain reagents you otherwise could not use. It does, however, require a deep analysis. You should only use it where it makes sense, but we see a big potential in this technology on the API side.
We are also discussing continuous manufacturing for Drug Product tablets.

What are your views on the potential realignment of manufacturing of antibiotics away from Asia to the West?

Should this capability be brought back to Europe? Yes, but in the end, somebody has to pay for it. If customers are not willing to increase the price, it will be a difficult discussion. ■

Insights on Manufacturing and Distribution

"Companies conducting their studies in China, mostly do so to have access to Chinese markets, so having facilities in both North America and China is a great benefit as it positions us to capture more growth opportunities. We can ensure the same quality standards, operating procedures and systems in both continents, while we still provide a detailed and highly experienced understanding of the regulations and requirements for drug discovery and development in both countries."

- Song Li,
Chairman & CEO,
Frontage Laboratories

"Trying to put social distancing in place in a manufacturing operation is not that easy and it leads to inefficiencies where you have to socially distance people or break up different processes. That affects our labor costs and bottom-line price to the customer. In addition, we have seen all packaging materials and components increase in price due to Covid. Whether it is bottles, caps, printed literature, everybody is passing on price increases."

- Joe Luke,
Vice President Sales and Marketing,
Reed-Lane Inc.

"Quality-driven projects prefer modular cleanrooms. When Nicos Group started to promote modular cleanrooms in North America in the 1990's, drywall cleanrooms still had approximately 95% of the market. It was quite interesting to see, as at the same time, modular cleanrooms already had 90% of the European market. It took some time to convince the North American market of the benefits of modular cleanroom systems."

- Francesco Nigris,
CEO,
Nicos Group

"If a client takes their compound through a single integrated process, they can reduce their time to proof of concept by 25%. You do this by having fewer handovers and through parallel processing... You are not reducing the time for each of the components, but you are reducing the time between them by overlapping them in a safe and efficient way."

- Chris Perkin,
CEO,
Altasciences

Generics

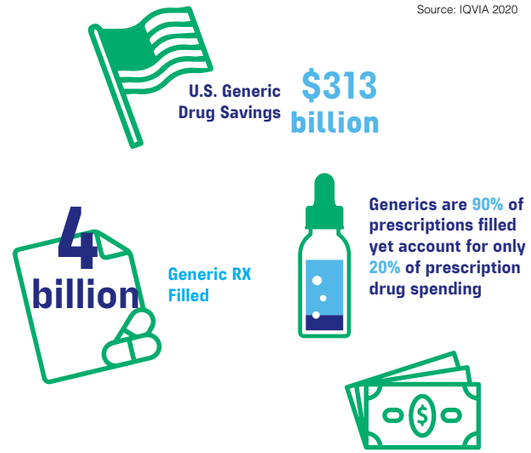
THE CHEAPER ALTERNATIVE

The tacit "social contract" between patients, payors and drug product innovators is that Americans will pay high prices initially for innovative medicines, but once a patent lifts on a product, generic drug companies must be allowed to find alternative ways to manufacture a competitor drug that should work indistinguishably from the brand name version. In a world of high prescription drug prices, cheaper generics have acted as a crucial counterweight. Bringing drugs to market as cheaply as possible while meeting and exceeding FDA standards makes for a difficult business model, however. The market has always been fiercely competitive, but has become exceedingly so since 2016, when the Generic Drug User Fee Amendments, or GDUFA, I and II, regulatory approvals were expedited. This caused the number of abbreviated new drug application (ANDA) approvals to increase considerably. According to BCG, 90% of the approvals have been for established products for which other ANDAs already existed. As a result, mature generics are hotly contested, and most become commodities within two to three years of launch. Moreover, consolidation among wholesalers has allowed buyers to demand lower prices.
In FY2020, the trend toward greater ANDA approvals was disrupted, as Covid forced the FDA to implement restrictions in conducting facility inspections and the agency diverted resources to respond to the pandemic. In doing so, FDA postponed hundreds of drug company inspections, creating an enormous backlog that delayed new drug approvals, leading the industry to warn of impending shortages of existing medicines. "This was a big problem for a company like ours as we currently have three CGT applications whose reviews are complete, yet we could not get them approved because the facility inspections were still pending," said Jay Shukla, president and CEO of Nivagen Phaceuticals.

When we first entered the market, only 20% of prescriptions dispensed in the US were generic, now a large part of the prescriptions that are dispensed are generic...Our main strategy in the US is to make sure we have an efficient cost of goods supply chain. We are looking at how to backward integrate in order to de-risk our supply chain and make sure that we are able to continuously supply good quality and quantity drugs in the US.

- Sharvil Patel, Managing Director, Zydus Cadila

Source: IQVIA 2020



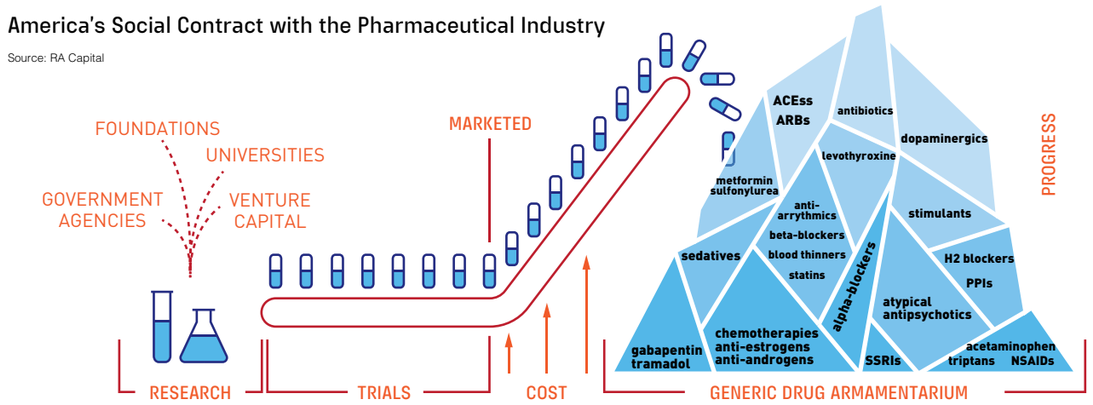
More Solutions Under One Roof

Amidst the pandemic, companies such as Nivagen continued to press on with plans to develop and grow their business by taking on new investors and deploying money to grow through acquisitions. Telegraph Hill Partners (THP) did a deal with Nivagen for US$16 million in growth equity financing to support future growth. Shukla explained that the impetus for choosing THP was because of their deep experience partnering with CDMOs. "The capital provides us with more flexibility in acquiring or investing in 505(b)(2) or ANDA programs. It also allows us to invest with our partners in new molecules, and it will facilitate the growth of our sterile injectables manufacturing unit," Shukla commented.
LGM Pharma is also adding CDMO capabilities to its repertoire. In July 2020, the company acquired Nexgen Pharma, a comprehensive drug product CDMO. According to LGM CEO Prasad Raje: "Because we service clients across therapeutic areas and regulatory pathways, and they often sought guidance for formulation development and drug product manufacturing, it was a natural fit for LGM to acquire CDMO capabilities. Our thinking was, since customers trusted us with one aspect of their business, it is a value-add to bring in development and manufacturing services – keeping it under one roof."

In order to control costs, many generic drug manufacturers turn to strategic sourcing, often from India, China and other locations where raw materials and labor can be less costly. They also work to form long-term relationships or cost agreements with suppliers. It is important, however, to strike a delicate balance looking for low-cost sources of essential raw materials, while also maintaining a high standard of product quality and availability. High levels of impurities or unreliable quantities of the material can derail projects and cost much more money due to product delays or failures in the long term.
Biophore, based in Pharma City in Visakhapatnam India, has filed over 100 drug master files (DMF), with a strong focus on peptides, contrast agents and oncology. The company has four API manufacturing facilities producing approximately 130 products, which operate at cGMP standards and meet the requirements of US and EU Drug regulatory authorities. The company's founder and CEO Jagadeesh Babu Rangisetty remarked: "I believe that Hyderabad is the capital of the pharma industry, especially on the API front. There is significant competition in the city which cultivates growth and quality. For the last couple of years, affordability, pricing and quality of drugs have been highly discussed topics. India plays a very significant role in terms of controlling prices and delivering affordable drugs to the US market."

America's Social Contract with the Pharmaceutical Industry

Source: RA Capital



Nationalism and supply chains

Over the course of the past year, API production became an overtly political issue, as the pandemic swept across the world exposing vulnerabilities in many API supply chains. Policymakers are now considering how to incentivize a more secure supply chain so drug shortages are prevented. President Biden has proposed that the US government take steps in the aftermath of the Covid-19 crisis to produce American-sourced and manufactured pharmaceutical and medical supply products in order to reduce dependence on foreign sources that are unreliable in times of crisis.

James Gale, CEO of Signet Healthcare Partners, acknowledged: "There was a real risk in Spring 2020 that, had production not restarted on a timely basis, there could have been serious shortages of supply of life-saving generic drugs. This near crisis has directed attention to the need to move the supply closer to home."

Although the idea of bringing API manufacturing back to the US appeals to many in theory, in practice, the execution will inevitably pose major challenges. Gale posed the question: "If the US is to create a domestic supply, will the market support it? Who is willing to pay the price associated with US production versus cheaper product from India? The current structure of the US generics market will have to be changed. Presently, there is little incentive for the distributors to support this national goal. I do not see economic players who are willing to finance repatriation of the drug supply chain to the US."

This situation, where the U.S. public demands rock-solid supply chain security delivering high quality, and, at the same time, lower and lower prices, is exceedingly difficult to achieve. Marc Kikuchi, CEO & Head of North American Generics, Dr. Reddy's Laboratories, contended: "One of the most problematic issues is the push by governments throughout the world to on shore API production and finished goods manufacturing. This global phenomenon, fueled by the rise of nationalism, will present unique challenges that generic pharma manufacturers – due to the sheer number and volumes of product we produce – will be grappling with this for many years to come."

With respect to how this could impact pricing, Kikuchi added: "Generic manufacturers are vilified in the press for price increases. What is not addressed is that manufactures may have higher costs for accelerated manufacturing or seeking alternate sources for APIs. Generic manufacturers cannot absorb all of those increases, so we have to pass these costs on to customers. A 250% increase may sound large, but this translates to US$6 or US$10 for a product."

All challenges aside, generic pharmaceutical drugs play an essential role in the US and global life science ecosystem. Right now, according to FDA reporting, 9 out of 10 prescriptions in the US are filled by generic drugs. Generics have also saved the health care system US$2.2 trillion dollars in the past decade. That is good news for the public health of Americans, and it is all the more reason why policymakers must be cautious and nuanced in implementing new policies that might reshape the generics landscape for the years to come. ■

The catch-22 to reshoring manufacturing and reducing dependency is that it can lead to higher costs at a time when the number of prescriptions is still weighted to generics to keep costs low. Therefore, a reshoring effort must be subsidized in some way... If we could come up with a list of critical medicines and only subsidize those, that could be a pathway for a sustained domestic infrastructure.

- Prasad Raje, CEO, LGM Pharma

Jagadeesh Babu Rangisetty

Founder & CEO
BIOPHORE

> We manufacture a lot of our own starting materials and have control over our supply chain, making us non-dependent on China.

Can you provide an overview of Biophore's specialization and the company's offering to the US market?

Biophore has been filing drug master files (DMF) since 2010, and as of 2021, we have filed over 100. We are now one of the leaders in DMF filings to the USFDA. Biophore has a very diversified portfolio, but our current focus is more on specialized fields such as peptides and oncology. Another area of strength for Biophore is contrast agents. We are very active in Europe, and now bringing these products to the US market also. We are investing heavily in these areas.

What makes the peptides and contrast media fields so appealing?

There are very few peptide manufacturers in India, but most of the generic industry today is dependent on India for their APIs. Peptides need specialized technology in terms of their characterization and manufacturing. Biophore believes that peptides are a good area to invest in, both in terms of the IP and manufacturing. The same goes for contrast agents.

Where are Biophore's manufacturing facilities located and what is the current focus at these facilities?

Biophore has four API manufacturing facilities, all located in Pharma City in Visakhapatnam. We manufacture approximately 130 products from these four facilities, which operate at cGMP standards and meet the requirements of US and EU Drug regulatory authorities. Each facility has a specialization -one focusing on large volume products; one on steroids, peptides, APIs, and macromolecular complexes; another on oncology; and one on contrast agents.

What has been the impact of Covid-19 on your business?

Biophore has been extremely fortunate as we have had a significantly good year in terms of growth during this pandemic. We have also not seen any negative impact in terms of business in the US market. We have been involved in manufacturing a Covid-19 drug called Favipiravir, and we are one of the leading manufacturers of this particular API. All starting materials and complex intermediates are either sourced locally or have been developed in-house for use. We manufacture a lot of our own starting materials and have control over our supply chain, making us non-dependent on China.

How does Biophore ensure the highest quality control practices are implemented in its facilities?

For Biophore, quality is paramount. We are focused on regulated markets with global specifications, and have therefore invested significantly in ensuring best quality practices in our facilities which meet international standards. We have different layers to our quality management systems and also have a corporate quality department which functions like an external agency monitoring our facilities.

Do you see India's growth making the domestic market a more viable end market for Biophore in the future?

We have been thinking of entering the domestic market for a long time, but this has not happened yet because of our focus on specifications for regulated markets. You cannot have two specifications for different markets, and you need to focus on one specification to maintain good quality standards. Having two specifications, one for the regulated market and one for the domestic market, compromises quality. For APIs that we want to introduce into the domestic market, we will build a separate facility which we hope will happen in 2021.

What is the importance of Hyderabad for the US market and can you speak to the role generics play in bringing affordable drugs to US consumers?

I believe that Hyderabad is the capital of the pharma industry, especially on the API front. There is significant competition in the city which cultivates growth and quality. For the last couple of years, affordability, pricing, and quality of drugs have been highly discussed topics. India plays a very significant role in terms of controlling prices and delivering affordable drugs to the US market, due to competition and the quality that can be delivered.

What is your vision for the company for the next 2-3 years?

Currently, Biophore is filing approximately 15-20 DMF per year. We want to accelerate this number and file at least 25 DMFs per year. This means that we will need some additional capacities and we are thus investing in a greenfield facility project where we will manufacture different kinds of APIs. We believe that this facility will be operational within the next year. We also want to increase our focus on key starting materials manufacturing on very selective high-volume APIs as to lessen our dependence on China. ■

Jay Shukla

President & CEO
NIVAGEN PHARMACEUTICALS, INC.

> At Nivagen, we want to bring manufacturing to the US, so our goal is to start our own manufacturing unit focused on sterile injectables.

How will the US$16 million growth equity financing Nivagen received in 2020 help support the company's future growth?
The reason we chose Telegraph Hill Partners was because of their deep experience partnering with CDMOs. At Nivagen, we want to bring manufacturing to the US, so our goal is to start our own manufacturing unit focused on sterile injectables. The capital provides us with more flexibility in acquiring or investing in 505(b)(2) or ANDA programs. It also allows us to invest with our partners in new molecules, and it will facilitate the growth of our sterile injectables manufacturing unit. The third advantage is that having a private equity partner of their reputation gives us credibility in the debt market. They also bring intangible values like governance, networking, wisdom, and experience, so, for us, they were the right fit.

What advantages will Nivagen have over competing manufacturers?
Currently many of the big multi-facility CDMOs do not understand the need for speed companies require, especially in generics. Second, a lot of CDMOs do not fully comprehend the cost of goods structure. A lot of these CDMOs have not really worked on their own with the FDA. We provide complete research, analytical formulation development, and importantly, we also provide regulatory support. Above all, we have experience in filing the application, so we know exactly what regulators expect and will request.

How has the pandemic impacted FDA inspections?
Until very recently, the FDA had essentially ceased conducting inspections in the US and abroad. Although some applicants had already completed their reviews, they were unable to receive FDA approval on their products. The only exceptions were those companies who had conducted pre-approval inspections, which is rarely the case. This means that many approvals were deferred and basically at a standstill. This was a big problem for a company like ours as we currently have three CGT applications whose reviews are complete, yet we could not get them approved because the facility inspections were still pending.
The great news is that the FDA just put out new guidance regarding the use of virtual inspections on April 14, 2021. The FDA and its employees have been working hard throughout the pandemic, and they have heard the voices coming from the industry. We are hopeful that with this new guidance we will have an inspection soon.

What is the current focus of Nivagen's business strategy?
We remain focused on molecules with supply issues, where there are fundamental challenges with the API, manufacturing, or packaging. The second area we focus on is on improving existing therapies with the 505(b)(2) program. We continue to look for ways to provide convenience to doctors and pharmacists through better dosage forms. We also have our own distribution platform through which we continue to launch and market products.

Can you speak to the role generics play in lowering the cost of drugs in America?
For every dollar we spend on drugs in the US right now, 90 cents are spent on branded products. In terms of volume, 90% of drugs are generics. Therefore, generics bring extraordinary value to government programs and insurance companies. In terms of incentives, I believe that the market is working on its own. I would not incentivize generic substitution, because if there is a new therapy with an advantage, or a newer molecule, it should not be stifled in order to promote generics. That would kill innovation.

How can US-based companies compete with generics companies in other parts of the world given their cost advantages?
It is extremely difficult to compete with a company in China or India if you are manufacturing in California. However, nowadays cargo, shipping and trucking costs have risen significantly. If you were to add a potential government incentive that favors local manufacturing on top of that, then US-manufactured companies would become much more competitive.
The issue we have is that the consumer does not see the savings because there are so many middlemen – the wholesaler, PBM, and insurance company – each getting a percentage. That is what is inflating the price and that is putting pressure on manufacturers to manufacture in lower cost jurisdictions. If there were a way to either reduce the middleman's exposure, sell direct-to-consumer, or direct-to-pharmacy, then the cost of manufacturing would not be a significant factor. ■

Robert Bloder

Chief Business Officer
ASCENDIA PHARMACEUTICALS

> Our growth strategy includes a strategic partner and we are pleased to have just announced that we received a growth PE investment from the esteemed Signet Healthcare Partners.

Can you provide us with an overview of Ascendia?
Ascendia Pharmaceuticals is a nine-year-old specialty pharmaceutical CDMO that provides custom sterile and non-sterile enabling formulations along with analytical methods for new chemical entities, complex dosage forms, and 505(B)(2) product development, as well as OTCs and nutraceuticals. The company has put together a suite of unique technologies and IP platforms to develop all dosage forms for new product development and GMP clinical trial materials.

What have been the keys to Ascendia's rapid growth over the past three years?
In the early stages, Ascendia distinguished itself as experts in poorly soluble molecules, which are about 60% of the new drug pipeline under development. The technologies and IP platforms that our founder and CEO Jim Huang put together not only differentiate us in the marketplace to bolster product IP, but they also allow us to work seamlessly with virtually every dosage form that is available. This flexibility is really important when we deliver on our promise to clients with formulations to the clinic and are able to quickly pivot to the next dosage form that is patient-centric and comports to our client's goal of maximizing market potential. In the past two years, our technical prowess, service-oriented culture and flexibility have begun to make the impossible possible for many companies. Building our reputation one project at a time, many of these clients have anointed Ascendia as a "Partner of Choice" because of the successes we've achieved for them, where perhaps others have fallen short.

Can you provide an example that illustrates Ascendia's effectiveness in helping clients?
In the past two years we've had the privilege to work with several fast-growing startups and big pharma clients. One client that was moving very quickly with an anticancer product that was working well for patients who had undergone multiple rounds of chemotherapy. Unfortunately, it required 50 to 60 pills per day, which was nearly as painful as the disease state itself and not tolerable. The company was about to lose their funding because it was not a viable option for these patients, despite the dire straits, they were in. Ascendia was able to improve the bioavailability and decrease the dose to 10 to 12 pills per dosing, which has provided for the project to continue with funding. Furthermore, the product's success has enabled the company to secure additional funding to support Ascendia's formulation development of an IV and ophthalmic. Ascendia's successes have added significant value to customer product portfolios and pipelines such that multiple projects with a client are becoming the "new normal" and "bread and butter".

What are the most important considerations for companies hoping for a successful development program?
Don't hope! Go with the best and get it right the first time. More time equates to delayed approvals, more money being spent and opportunity loss for patients in the commercial market. It has been well described that big pharma has been killing projects earlier so they can reallocate resources and go forward with the most promising compounds and formulations. It is even more important for a company that has a molecule and is focusing in rare disease to get it done right the first time in as robust a formulation as possible. Many CDMO's and companies have formulation capabilities, but when the product runs into a snag or an issue, who has the domain expertise to solve those problems with a partner? Who has the tribal knowledge to share about the molecule itself (that they are passionate about) to move through those issues quickly and efficiently? That is something that requires not only the tactical prowess, but the employees and culture how they interact to collaborate with these domain experts who are passionate about their molecules.

What is Ascendia's long-term vision?
Ascendia has been bootstrapping for the past nine years with a friends and family round. Our growth strategy includes a strategic partner and we are pleased to have just announced that we received a growth PE investment from the esteemed Signet Healthcare Partners to grow and expand our people, capabilities and facilities to meet and exceed customer expectations from early to late state development. ■

Sharvil Patel

Managing Director
ZYDUS CADILA

How is Zydus Cadila's business positioned for the coming decade?
We see four pillars of growth. First, the business will be strongly driven by drug discovery and innovation. Second, patient centricity will be an important area in terms of how we design our programs for outcomes. Third, we intend to hone in our efforts to digitalize our capabilities both in the front and back end to be able to reach more customers in a better fashion. Also, Covid taught us that having a strong diversified infrastructure aids in overcoming challenges.
As we transition from a pure generics company to a branded generics company, we believe access and affordability will continue to play a key role in our growth story. However, drug discovery and innovation will drive the future growth for the organization. These innovations will be outcome driven. We will work across areas like vaccines, biologics, small molecule research, and transdermal injectables. This strategy will be modeled off of our success in generics, where we have 400 plus ANDAs in the US.
We will also have a large pipeline of products that meet the access and affordability criteria. A large part of substitution happens today in the US once the patents expire, and we will build onto that. Meanwhile our strategy in India, is to be more therapy specific. We intend to launch new therapies in the areas of Non Alcoholic Steatohepatitis (NASH), Oncology, Renal Care, and Autoimmune diseases.

As the 4th largest pharma company in the US, how has Zydus Cadila adapted to meet customer needs?
The generics market in the US has been a mainstay for Zydus Cadila's business and it has transformed substantially in the last couple of decades. Our main strategy in the US is to make sure we have an efficient cost of goods supply chain which can meet the demands of the US market. We are looking at how to backward integrate in order to de-risk our supply chain and make sure that we are able to continuously supply good quality and quantity drugs in the US. R&D must be productive, and we believe we should be filing 30 to 35 new drug applications (NDAs) every year in the US from a generics point of view. Today, we are largely an oral solids company, but we are transitioning towards more complex products like transdermals. A large part of our portfolio in the future will be driven by complex injectables.

Zydus is developing a novel vaccine in ZyCoV-D. How did you choose this platform and did you have the in-house capabilities to develop this?
Zydus has more than 300 scientists who work on vaccine research, so it is an area we have great expertise in. We were the first Indian company, and the third in the world to develop and commercialize the Swine Flu vaccine in 2010, and we have worked to develop several other vaccines.
Over the past year, we developed a vaccine for Covid-19, which is based on a DNA platform. It is currently in phase three clinical trials and is being tested on around 30,000 volunteers. In the Adaptive Phase I/II trials we received strong safety and immunogenicity data. In the Phase III trials we will ascertain the efficacy of the vaccine. Once launched, ZyCoV-D will reinforce this fight against Covid both in India and other countries in need of vaccines.

What are the advantages of the DNA platform used in ZyCoV-D?
One of the reasons we chose this platform is we believe that when the body of evidence is low, safety will be one of the important markers for selection of a vaccine. We saw very strong safety markers when it came to this technology on DNA. A second factor was that it is much simpler to manufacture because it has minimum biosafety requirements. Therefore, one can easily find facilities. Also, a lot of vaccines are vectors which elicit immune response. Our vaccine is devoid of any vectors that are present in the plasmid.
Further advantages include the fact that as mutations occur, this platform enables us to change the sequence of the virus very quickly. Finally, there is vaccine hesitancy when it comes to taking injections, but ours is an intradermal device and not an injection. It is a small application on the skin, devoid of any major side effects and it is painless to administer. ■

Marc Kikuchi

CEO & Head of North American Generics
DR. REDDY'S LABORATORIES

By the end of next year, we expect to sustain our annual launch momentum of close to 30 new products in multiple disease categories.

What were some of the key developments for Dr. Reddy's in North America in 2020 and which segments of the business are the largest drivers of revenue?
Despite the global headwinds caused by Covid-19, Dr. Reddy's (DRL) was able to continue its re-growth in North America moving from 12th to 9th according to IQVIA prescription data. In 2020 DRL launched over 30 new products and was able to provide consistent supply on over 90% of its product portfolio to its customers. Retail pharmacy continues to be a critical segment for DRL in North America and our OTC portfolio continues to expand and gain momentum. We focus on Rx to OTC switches and just launched five new products over the course of year, but remain the only company in the US to launch OTC versions of both generic Voltaren (diclofenac gel) and generic Pataday (olapatadine). Both of these brands switched to OTC in early 2020.

Can you elaborate on Dr. Reddy's focus on complex generics delivery in North America?
At Dr. Reddy's, we are focusing on our core capability, which is manufacturing generic pharmaceuticals. Given our expertise in the market, we are also bringing more finished dosage forms to market beyond tablets and capsules. We are moving into injectables, and even more importantly, complex injectables that are drug-device combinations, as well as patches, creams and ointments.
An emphasis on the full spectrum of generic products, including complex generics, means we will need to reimagine our Go-to-market approach. We will need to "Go Beyond the Pill" in our commercialization efforts to increase access for patients and increase adherence.

Do you anticipate more reshoring of API production in the US?
The pharma industry in general, and generics manufacturers in particular, face an array of unprecedented challenges in the wake of the Covid-19 pandemic. One of the most problematic is the push by governments throughout the world to on shore API production and finished goods manufacturing. This global phenomenon, fueled by the rise of nationalism, will present unique challenges that generic pharma manufacturers – due to the sheer number and volumes of product we produce – will be grappling with for many years to come. Maintaining high-quality standards for API and finished drug forms in an ever-evolving supply chain landscape is underpinned by the requirement for environmental preservation, resource availability and urgent need to deliver sustainable manufacturing. Because of this, I predict that sustaining the environment will become the No. 1 challenge for manufacturers and supply chain participants in the pharma industry over the next 10 to 20 years and beyond.
I am not sure if it is feasible or practical to onshore API production and finished goods manufacturing for all products. I think there are some drug classes that the US may want to reduce its reliance upon offshore global supply chains such as antibiotics and antivirals. For most other products, there is sufficient global capacity to meet demand and thus a more practical solution may be increasing safety stocks levels at US-based distribution centers across the supply chain from manufacturers to wholesalers/distributors to pharmacies.

What role does Dr. Reddy's play in bringing affordable drugs to market in the US?
We launched the generic Suboxone in June 2018 for the treatment of opioid abuse and it is in a sublingual form that fulfills an important patient need for an affordable generic alternative. We also established our presence on Amazon with a portfolio of over-the-counter products that are becoming quite successful, especially in Covid times.

What long term growth opportunities is Dr. Reddy's pursuing?
We are waiting for FDA approval or feedback on more than 100 abbreviated new drug applications. By the end of next year, we expect to sustain our annual launch momentum of close to 30 new products in multiple disease categories. Many of these products will be complex or difficult to make, and they will fall in the limited competition space.
From a global perspective, Dr. Reddy's is focused on growing in specific markets such as North America, India, China, Russia and Europe. DRL continues to expand its API business and plans to leverage its growing injectables portfolio on a global scale. With regards to other growth areas, DRL is also investing in furthering its biosimilars and specialty pharmaceutical programs. ■

During our research, we speak to business leaders across the value chain to gain a qualitative understanding of the state of the pharmaceutical and biopharmaceutical industries based on their experiences. Through what amounts to several hundreds of conversations, we compile a database of valuable knowledge on a range of important topics. In these pages, please find a brief selection of quotations that we feel best summarize some of the challenges the mining community should expect to encounter going forward, the opportunities to find success, and also thoughts we found to be motivational. Thank you to all of the individuals that took the time to share their insights with us, and we look forward to continuing to learn from you in the years to come.

It is extremely challenging to start a company from scratch, particularly if it is an R&D-based company, and within R&D, particularly so for pharmaceuticals. The demands are high, but so are the financial rewards, and the psychic rewards of improving outcomes of patients suffering debilitating and potentially fatal diseases cannot be matched in any other industry.

- Brian Frenzel, President & CEO, Tosk

The last four years have been the easiest capital environment for biotech in terms of raising capital, building companies, and most recently, taking companies public either directly or via SPACS. Capital has been available for biotech assets and science has moved forward at a breakneck speed. What is missing broadly in biotech is human capital. You cannot triple the number of publicly traded biotech companies and continue building teams. There is simply not enough talent out there. Our biggest challenge is continuing to scale and grow the company while attracting high quality talent. That has become the rate limiter to growth in the sector.

- Amit Munshi, President & CEO, Arena Pharmaceuticals

"In the US you have a lot of very dynamic biotech companies with entrepreneurial spirit and very fast decision making. There is also more risk-taking. In Europe, taking risks is less common for cultural reasons, so we have big pharma companies that typically take much longer when working together."

- Michael Quirmbach, CEO & President, CordenPharma

"We are thinking about the genomic and genetic data that is available and how to bring that back into the discovery cycle. This gives us much better insight in terms of how to predict and identify drugs that will be successful in the clinic."

- Jay A. Roberts, President & CEO, Vyant Bio

"BARDA and the Gates Foundation care about scalability, among other considerations. For a product to be considered for addition to the National Strategic Stockpile, or for use in the developing world, one has to imagine a path to produce a fairly large number of doses at a cost that is not prohibitive."

- Bernat Olle, CEO, Vedanta Biosciences

"As an entrepreneur, I was interested in how academic breakthroughs get translated from basic science to the point where they impact patients. There was an existing ecosystem in place and usually it entailed an entrepreneur or scientist advancing one specific idea. The most compelling entrepreneurs and scientists get funding and there is attrition along the way. What occurred to me was that at the beginning of the process, those individuals were advancing their own ideas but not necessarily looking broadly and asking what the best idea is."

- Daphne Zohar, Founder & CEO, PureTech Health

"The impacts of Covid-19 have brought the realities of managing complex supply chains—including the potential risks and instabilities that it can present—to the forefront for life sciences companies. It created an opportunity for many businesses to re-evaluate the management of their supply chain, identify redundancies, and potentially introduce new processes or duplicate partners to create a more resilient supply chain. Across all industries, companies should be having the important conversation about how their supply chain will be managed based on a series of worst-case scenarios."

- Peter Meath, Managing Director, Co-Head of Healthcare and Life Sciences, Middle Market Banking & Specialized Industries, J.P. Morgan Commercial Banking

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