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FEBRUARY 2018

STEVEN PAUL, M.D.
CEO, Voyager Therapeutics

The Intriguing Origins Of A Gene Therapy Biopharma

p. 18

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CONTENTS

Welcome to

Life Science Leader

FEBRUARY 2018 VOL. 10 NO. 2

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18 Cover Story: VOYAGER THERAPEUTICS

An inside look into how this fledgling biopharma has raised over $150 million and enlisted two high-profile CEOs from one of the hottest VC firms around, all in less than two years

Features:

22 The Enterprisers

In this series on "Life Science Leadership In Action," we discuss PolarityTE, which focuses on regenerating lost tissues in their original complex forms.

38 The Art Of Leadership

Former Pfizer exec and current partner at VC firm Polaris Partners Amy Schulman talks about what it takes to lead a pharma startup.

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How To Stop Biopharma's **Negative Reputation Tailspin**

ROB WRIGHT Chief Editor

Over the years I have attended many biopharmaceutical industry meetings. During these gatherings, I often hear executives lament how an industry that has done so much good, for so many and for so long, can be universally reviled. Not long ago, the biopharmaceutical industry was the *most* admired and respected in the world. But here's an interesting factoid we need to wrap our heads around: Since 2001, when Gallup began annually testing the views of major business and industry sectors, the public's perception of the pharmaceutical industry has only been positive three times (2001, 2003, and 2014)! And since 2003, when Gallup expanded the list to 25 industries, pharma has consistently ranked in the bottom third.

But in Gallup's 2016 ranking, the pharmaceutical industry reached a new low, receiving negative ratings by more than half the public, achieving a net score of -23 (the difference between total positive and total negative perceptions). The only industry that did worse was the federal government, which tallied a -27. In Gallup's 2017 poll, pharma once again ranked second from the bottom, -17, beating out the federal government's tally of -23. But let's not start high-fiving one another for being hated less last year, for out of 25 industries, only four had negative scores, with the other two being oil and gas, -2, and healthcare, -7. The computer industry (ranked #1 in 2017) had a net positive Gallup score of +67, which was achieved following a year of scandals (e.g., Samsung's Galaxy Note 7 exploding, 500 million Yahoo user accounts being hacked).

If the computer industry can obtain *the highest* positive perception ranking despite these and other negative industry news, why can't biopharma do the same? We've cured Hepatitis C. We've cured half of all cancers, and yet we've never been so despised. Has our continual focus on all we've done right blinded us to the impact of everything we've done wrong? Perhaps it is time we stop blaming others (e.g., health insurers, media, politicians) and admit that we have met the enemy to our public perception maladies, and it is us. So what do we do about it?

Last February, *The Harvard Business Review* published "How Pharma Can Fix Its Reputation and Its Business at the Same Time" by Damiano de Felice, deputy director of strategy at the Access to Medicine Foundation. He recommends transforming "access to medicine" from a relentless activist slogan to full-fledged business strategy. De Felice notes that investors are increasingly interested in how biopharmas are managing access-to-medicine opportunities and risks. Improving access to medicines is viewed as a sustainability initiative (by BlackRock, Morgan Stanley, and others) that can yield opportunities for growth, innovation, and unique partnerships that can enhance shareholder value. While improving access will likely benefit our industry's image, it will all be for naught if we don't also address other challenges that have plagued our past, such as egregious drug price increases, corruption, collusion, deception, and unethical marketing practices. L

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Q What are the greatest challenges facing our industry, and what are companies and our industry doing to meet such challenges?

A ASYMMETRY IN THE PHARMA BUSINESS MODEL. A belief that, unlike R&D, we must continue to own all elements of the commercial model. It's draining our resources. Commercial success requires analytics, promotion, and contracting among many other diverse functions. Owning these commercial functions "front to back" is suboptimal and should be reconsidered.

An integrated commercial model sourcing expertise that can be toggled on/off (akin to CROs) is a logical step. This modular approach would provide highly skilled commercial talent, enhance commercial efficiency, and result in improved return. Ultimately, this model would free up capital to fund clinical innovation and improved patient care. Building greater flexibility into the commercial infrastructure is key to continued success for the industry and providing innovative therapeutic alternatives to patients.

RICH DALY
is chairman, CEO, and president of Neuralstem, Inc., a public company (NASDAQ: CUR) enabling commercial-scale production of multiple types of CNS stem cells.

Q Why are 505(b)(2)s gaining increased interest among midsize biopharma companies?

A THE 505(B)(2) NEW DRUG APPLICATION (NDA) encourages sponsors to file somewhat streamlined regulatory submissions in which at least some of the information relies on the FDA's findings of safety and effectiveness of a similar, previously approved, reference drug and data available in the public domain. A 505(b)2 NDA contains bridging studies comparing the new drug with the reference drug. In addition, sponsors must still provide preclinical or clinical data to ensure that the new formulation/form/route of administration does not compromise safety and provides efficacy. This effective business model takes less time, cost, and risk to get product onto the market because the active ingredient has been previously approved with data from a prior submission package. Depending on the extent of the change to the previously approved drug and the type of clinical data included in the NDA, it is possible to qualify for three or five years of market exclusivity for the new drug.

MITCHELL KATZ, PH.D.
is head of clinical research and drug safety operations at Purdue Pharma L.P.

Q In your role as a biopharmaceutical angel investor, what are some questions you ask and why?

A I ASK THREE QUESTIONS about a compound: Can it be made? Is it safe? Does it work? Obviously, there are no definite answers at an early development stage, but likelihood of a "yes" needs to be assessed. I am *not* asking for predicted peak sales evaluation (or anything similar) because it is a nonsensical number anyway. Most compounds that meet the above criteria will exit with at least a decent return to early-stage investors. I also ask if the "story" is simple. Complex science produces wonderful publications, but not very often does it translate to useful medicines. I also ask the founders a few questions to get a sense of their commitment to building value.

TOMASZ SABLINSKI, M.D., PH.D.
is cofounder and CEO of Transparency Life Sciences.

Government's Absurd View Of The Healthcare System

JOHN MCMANUS The McManus Group

The absurdity of the U.S. government's perspective on the implementation of government-run health programs came into focus recently in the Republican tax overhaul bill as well as the rollout of the new Medicare physician payment system.

REPEAL OF INDIVIDUAL MANDATE GREASES ENACTMENT OF TAX REFORM

Republicans seized on the Congressional Budget Office's (CBO's) view that repeal of the individual mandate tax for failure to maintain health coverage would save taxpayers $338 billion over 10 years and inserted that provision into the tax reform legislation that was enacted in December. That provision enabled them to jam in substantially more tax breaks for corporations and individuals and still fit into their prescribed $1.5 trillion deficit-adding package.

Just as important, it was a twofer because it removed one of their most detested provisions in Obamacare, upheld by the Supreme Court in the landmark *National Federation of Independent Business vs. Sebelius* decision: the ability of the government to mandate purchase of a private good.

But how could repeal of the mandate tax — while leaving the actual mandate requirement in place — result in such a significant decline in government spending? CBO explains that such a policy would eventually result in 13 million more uninsured within 10 years and the associated subsidies for exchange insurance plans and for Medicaid, the program for the poor.

Let's unpack this.

CBO predicts the absence of a mandate tax that never applied to poor people enrolled in Medicaid will compel 5 million to quit the free healthcare available in that program. Individuals who are poor enough to qualify for Medicaid do not pay federal income taxes and therefore have never paid the tax penalty for failing to enroll in Medicaid. Yet CBO would have us believe that 5 million will disenroll because of the repeal of that tax?

CBO also projects another 5 million would quit the heavily subsidized coverage available in the Affordable Care Act's insurance exchanges. Yet the Kaiser Family Foundation found that 70 percent of subsidy-eligible individuals could get a "bronze" plan — the cheapest option available on the exchanges — for less than it would cost to pay the penalty tax. In fact, 54 percent could get a bronze plan for free! Nonetheless, CBO holds firm to its irrational notion that individuals would act in ways detrimental to their own interest.

Similarly, CBO projects another 2 million will quit their employer-provided coverage, which is primarily financed by employers. The employer mandate, which provides penalties to any employer with more than 50 employees that fails to provide coverage, has not been changed.

REAUTHORIZATION OF CHIP

CBO's bizarre projections were amplified in its recent evaluation of the budgetary impact of extending the Children's Health Insurance Program (CHIP), which expired at the end of 2017. Partisan squabbling over how to finance a five-year extension of that program (which has broad bipartisan support) had held up reauthorization last fall. Prior to the mandate repeal, CBO had projected a five-year CHIP extension to cost $8 billion. Then, in January CBO said such an extension would cost one-tenth that amount — $800 million — due to repeal of the individual mandate.

A week later, CBO elaborated that a 10-year extension of the CHIP program, which should intuitively cost twice as much for double the time, would actu-

ally *save* $6 billion over 10 years! CBO explains, "Extending CHIP yields net savings to the federal government because the alternatives for that coverage are more expensive than CHIP." Repeal of the mandate would lead to disenrollment of healthy individuals that would, in turn, drive up premiums to those who remain in the exchange.

"It's like manna from heaven!" declared a senior Republican committee staffer. We should have repealed the mandate years ago! As this column goes to press, resolution of the CHIP reauthorization is imminent.

THE WEIRD IMPLEMENTATION OF PHYSICIAN PAYMENT REFORM

The U.S. government's tortured perspective on the healthcare system is not harbored exclusively by the CBO. CMS' latest regulation implementing the new Medicare payment system for physicians authorized by the Medicare Access and CHIP Reauthorization Act (MACRA) is similarly perplexing. MACRA created two payment regimes for physicians: Alternative Payment Models (APMs) and the Merit-Based Incentive Payment System (MIPS).

The vast majority will be enrolled in MIPS for the foreseeable future. Physician practices are rated on a scale from 1 to 100 for performance related to quality metrics, utilization of electronic health records, and resource use. The law puts 5 percent of physician payments at risk in 2018, and that gradually rises to 9 percent over several years. Those practices that perform poorly are subject to penalties, which fund bonuses of high-achieving practices under a zero-sum game.

But because CMS excluded more than 60 percent of all clinicians from the program under various discretionary criteria such as low volume and hardship, the pool of money for the incentive program is extremely constrained: just $118 million in 2018. That is on a base of over $70 billion of total physician spending. This means there is very little incentive for practices to improve health delivery, and the practices that had invested significant resources to get ready for the new payment system now feel they squandered resources with little or no payoff.

More troubling, CMS chose to grade physician practices on a substantial curve, resulting in less than 3 percent of physicians receiving negative adjustments. That miniscule group of poor performers — who had scored less than 15 on the 1 to 100 scale — must pay penalties to fund bonuses for the 97 percent of winners. Result: The winners get virtually nothing — around $200 each annually.

CMS even undermined the MIPS program to recognize "exceptional" physicians by making any practice that scored a minimum of 70 out of 100 eligible for the $500 million pool of resources. (Only government would characterize a C minus score as "exceptional!") In doing so, it disregarded the clear statutory intent of limiting bonuses for "exceptional performers" to the top 25 percent of practices above the median. Result: The typical $6,600-per-physician bonus for exceptional performers (i.e., real money) plummets to about $1,100 because CMS bizarrely defined nearly 75 percent of physicians as "exceptional." If everyone is exceptional, no one is exceptional.

The Medicare Payment Advisory Commission (MedPAC) recently opined that MIPS cannot succeed and should be repealed. It reasoned that MIPS is burdensome and complex, much of the reported information is not meaningful, scores are not comparable across clinicians, and payment adjustments are minimal in the first two years and large and arbitrary in later years. MedPAC concluded, "MIPS will not succeed in helping beneficiaries choose clinicians, help clinicians change practice patterns to improve value, or help Medicare reward clinicians based on value."

The other program under MACRA — APMs, which is seen by policymakers as the future of healthcare because it encourages physician practices to accept capitated payments for value-based delivery arrangements — is fraught with even more problems. Less than 5 percent of physicians are enrolled in such arrangements, and most of those are in mostly hospital-led accountable care organizations (ACOs) that have failed to deliver any savings to Medicare.

The newly created Physician Technical Advisory Committee (PTAC) has approved only six APM applications of the 21 submitted, and four of those were for limited scale testing only. CMS has approved exactly zero of those applications.

MACRA was seen as landmark legislation to fundamentally reform physician delivery reform. It is essentially dysfunctional by any rational measure. Perhaps CBO can render similarly favorable budgetary projections for making necessary changes to this program as it provided for repeal of the individual mandate. L

JOHN MCMANUS is president and founder of The McManus Group, a consulting firm specializing in strategic policy and political counsel and advocacy for healthcare clients with issues before Congress and the administration. Prior to founding his firm, McManus served Chairman Bill Thomas as the staff director of the Ways and Means Health Subcommittee, where he led the policy development, negotiations, and drafting of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. Before working for Chairman Thomas, McManus worked for Eli Lilly & Company as a senior associate and for the Maryland House of Delegates as a research analyst. He earned his Master of Public Policy from Duke University and Bachelor of Arts from Washington and Lee University.

What Drug Developers Can Learn From Silicon Valley

DAVID JOHNSON, PH.D., MBA

I think Silicon Valley's most valuable asset is a ruthless focus on experimenting with product-market fit. Silicon Valley software companies have the mentality of pushing out products, getting market feedback, and then going back to the drawing board if the market responds poorly. Imperfect products are a learning experience — an experiment — rather than a reason to close shop or fire people.

As a graduate student and postdoc at Stanford in the early 2000s, I often looked with envy at friends getting rich by selling their software companies for tens of millions of dollars a year after founding. Besides the obvious financial rewards of software startups, the speed of progress blew me away. Even in academia, students who worked in software would often finish their degrees two to three years before students who slaved away at the bench. How could biotechnology, and bench-science companies in particular, possibly iterate as quickly as the software industry?

YOU NEED A COMPELLING BUSINESS PLAN AND DATA

I founded GigaGen in 2011. In classic Silicon Valley style, I initially worked out of my garage and had no cash. All I had was a Ph.D. in genetics and a drive to find better ways to analyze immune repertoires.

While I continued to lead the company with a Silicon Valley mindset, I relied on life sciences growth vehicles to fuel my next steps. First, I raised seed financing from a local VC and won a few NIH grants. I hired smart scientists and engineers to solve the technical problems. I also filled an advisory board with smart academics from Stanford. We filed patent applications. After two years, we reduced the technology to practice and generated a compelling data set. Unfortunately, our business plan was not as compelling as our data. As a result, I went through the painful process of laying off staff.

Without staff to manage, I had little else to do but reach out to anyone and everyone who would talk to me. By necessity, I was like an Apple product manager showing the latest beta-release iPhone to dozens of opinion leaders. I met with several people a day, showing them my data and asking for advice on how to apply the new technology.

The results were startling. It became clear that it was extremely effective to hypothesize use cases — in this case, drugs — and then ask interviewees for their thoughts on those hypothetical use cases. If I only showed off the technology and told them how useful I thought it was, they would nod but would not provide any insight. I needed to do experiments. I needed to test hypothetical uses as systematically and rigorously as the experiments I was used to doing at the bench.

Eventually, I hit upon three specific use cases that got very specific people very excited. One application was in the field of plasma-derived antibody therapeutics. Plasma-derived antibody therapeutics, specifically intravenous immunoglobulin (IVIG), is a $10 billion industry that has seen little innovation in decades. I found strong interest to use my technology to make a recombinant IVIG alternative to plasma IVIG. Another application was the replacement of hybridoma-based screening of mouse repertoires for discovery of checkpoint inhibitor drugs. I found that many checkpoint inhibitor programs were struggling to tease good antibodies out of mice, since checkpoint inhibitor targets are often not highly immunogenic. Finally, I found a strong interest from the T-cell community. I heard that the T-cell community was eager for new technologies to help them develop cellular therapies. It was difficult to get the T-cell groups to verbalize their needs — they just wanted "more" and "better" data — but by showing them a hypothetical product that my technology could

generate, and constantly asking questions, I began to uncover their needs through a series of iterative "yes" and "no" responses from dozens of experts in the field.

> *"The Lean Launchpad process literally saved us tens of millions of dollars and several years by homing in on a product that customers actually wanted, versus what we thought they would want."*

With these three product applications in hand, I applied for several NIH grants and won millions of dollars to finance the three product directions. Around the time that these grants started, NIH launched a new program called "I-Corps." This program is a commercialization accelerator based on a methodology called Lean Launchpad, which was developed by serial entrepreneur and Silicon Valley guru Steve Blank. NIH had recruited Steve Blank to adapt Lean Launchpad specifically for new biotechnology companies. In his program, teams — composed of key executives from the company — interview more than 100 potential customers, or experts, within 10 weeks. The idea is that after more than 100 interviews you should have refined your product to fit market need based on feedback or decided to drop the product entirely. The process is similar to what I had already been doing organically, but more organized and supported by mentors and peers.

The results were again startling. The Lean Launchpad process literally saved us tens of millions of dollars and several years by homing in on a product that customers actually wanted, versus what we thought they would want. Most importantly, we very specifically defined the "minimal viable product" for each research program. After hundreds of interviews, we were introduced to business development executives for Barcelona-based Grifols, one of the original and leading producers of plasma IVIG. We had already spoken to countless experts in plasma IVIG and had already progressed our laboratory data package through an NIH grant. Fortunately, the executives were impressed and described our company and technology to their bosses, which led to a $50 million financing and codevelopment deal in July 2017. Normally, a company might raise tens of millions of dollars to achieve such a milestone, but we only spent $225,000 of NIH money. Clearly, the Lean Launchpad process saved us millions of dollars and brought our impactful innovations to a Big Pharma that saw future commercial value.

A NEW FOCUS ON COMBO DRUGS

Our experience with recombinant IVIG was so powerful, we went through the NIH I-Corps process (i.e., an eight-week program providing funding, mentoring, and networking opportunities to help commercialize promising biomedical technology) a second time — for our immuno-oncology programs. Unlike recombinant IVIG, immuno-oncology is an extremely competitive and crowded field. Our challenge is to differentiate ourselves from this crowd. We found that most new companies in the immuno-oncology antibody field focus exclusively on a single target, whereas Big Pharmas have moved vigorously toward drug combinations against multiple targets. It became clear we needed to structure our drug discovery and development programs around combinations. Thus, we are currently using our T-cell expertise to test combinations of antibody drug candidates against 16 different targets.

Much has been written about innovation challenges at large pharmaceutical companies. Small biotechnology companies are in the business of innovation to help fill this gap. We specifically work with bigger companies to help them with their innovation challenges. Thus, surprisingly, in early stages, we are not just innovating for doctors and patients, but also for a third customer — the large partner company. To find what the partners are looking for, we can use methods such as the Lean Launchpad to determine product-market fit with precision. Though biotechnology may never be as fast and efficient as software, we can make innovation and development faster — through nothing more than a Silicon Valley way of thinking. L

GigaGen CEO DAVID JOHNSON, PH.D., MBA, is an inventor, entrepreneur, and expert in single-cell genomics with a track record of bringing new medical technologies to market.

Zavante

Challenging drug resistance with a retooled antibiotic and a broad mechanism of action

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Zavante has completed a pivotal Phase 2/3 trial of its lead broad-spectrum antibiotic drug, ZOLYD (fosfomycin injection), for treating complicated urinary tract infections (cUTI) and expects to file a new drug application for the product in mid-2018. Fosfomycin has a long history outside the U.S., but the company has recast the injectable to improve its pharmacokinetics and pharmacodynamics against acute infections in a hospital setting. ZOLYD has a unique mechanism of action and is targeted at GRAM-positive and GRAM-negative infections, including those caused by multidrug-resistant bacteria.

WHAT'S AT STAKE

Mechanisms matter. With any drug that employs a unique action or targets a disease pathway, the issue of drug resistance may arise. The principle is never clearer than with antibiotics, where time is running out for existing drugs because of the adaptations microbes have been, are now, and will be developing to them. Turning away from the therapeutic challenge and the troublesome economics of the antibiotics market, large pharma companies seem to be letting companies like Zavante take on the initial risk in drug R&D.

Zavante believes its lead product has a key advantage in that respect. Put simply, ZOLYD has a low molecular weight, which enables it to pass readily through porin channels. Once inside the bacteria, however, the drug irreversibly attaches to a single enzyme called MurA to block an early step in the bacteria's cell-wall formation. The unique mechanism of action means the drug avoids causing cross-resistance with other antibiotics. In their past use against chronic infections, the market for previous fosfomycin products by Merck and others faded as newer drugs entered. Zavante's scientific founder and anti-infective expert, Dr. Evelyn Ellis-Grosse, hit on the idea of resurrecting the drug for treating acute drug-resistant infections. Her concept included optimizing its IV form through well-established pharmacokinetic/pharmacodynamic principles and making it available for use in the U.S. The acute setting also potentiates another well-known advantage of fosfomycin — its synergistic action in combination with other common antibiotics — an ability that may help overcome growing bacterial resistance to some of those drugs as well.

Because fosfomycin has left a long trail of clinical data, Zavante succeeded in qualifying it for the FDA's accelerated 505(b)(2) pathway. But even that regulatory advantage would have been useless without the GAIN (Generating Antibiotic Incentives Now) Act of 2012, according to the company's president and CEO, Ted Schroeder. "There was a regulatory path, but really no economic path for bringing our product to the U.S. market," Schroeder says. "It had only three years of exclusivity remaining, and the patents had long ago expired. But when Congress passed the GAIN Act, which would give us an additional five years of exclusivity, Dr. Ellis-Grosse quickly went to Europe, found the manufacturer, and signed an exclusive product license for the United States."

Ellis-Grosse explored new career challenges in becoming a company founder, but she moved the product through a Phase 1 study financed by an NIH grant. That created a lot of enthusiasm for the product in the U.S., but not a lot of capital at first. In 2015, the founders acquired Zavante and recapitalized the company, began building its manufacturing capability, and secured the faster FDA pathway. The accelerated route required only a single pivotal Phase 2/3 study for approval, which ended successfully in mid-2017. Its pipeline contains three other targeted indications at an early clinical stage and numerous others in preclinicals. Although this column usually does not cover companies with "repurposed" drugs in development, Zavante is a useful exception to illustrate another important strategy in the critical, but underserved, antibiotics space.

Ted Schroeder
President & CEO

Vital Statistics

10
Employees

Headquarters
San Diego

Finances

$45M
Series A Round

Investors
Frazier Healthcare Partners, Longitude Capital, Aisling Capital

Partners
National Institute of Allergy and Infectious Disease (NIAID), to evaluate ZOLYD in hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) infections

Latest Updates

September 2017
Announced planned Phase 1 trial with NIAID to assess the intrapulmonary penetration and pharmacokinetics of ZOLYD to treat HABP and VABP infections. The U.S. FDA has granted Fast Track and Qualified Infectious Disease Product (QIDP) designations to ZOLYD for both indications.

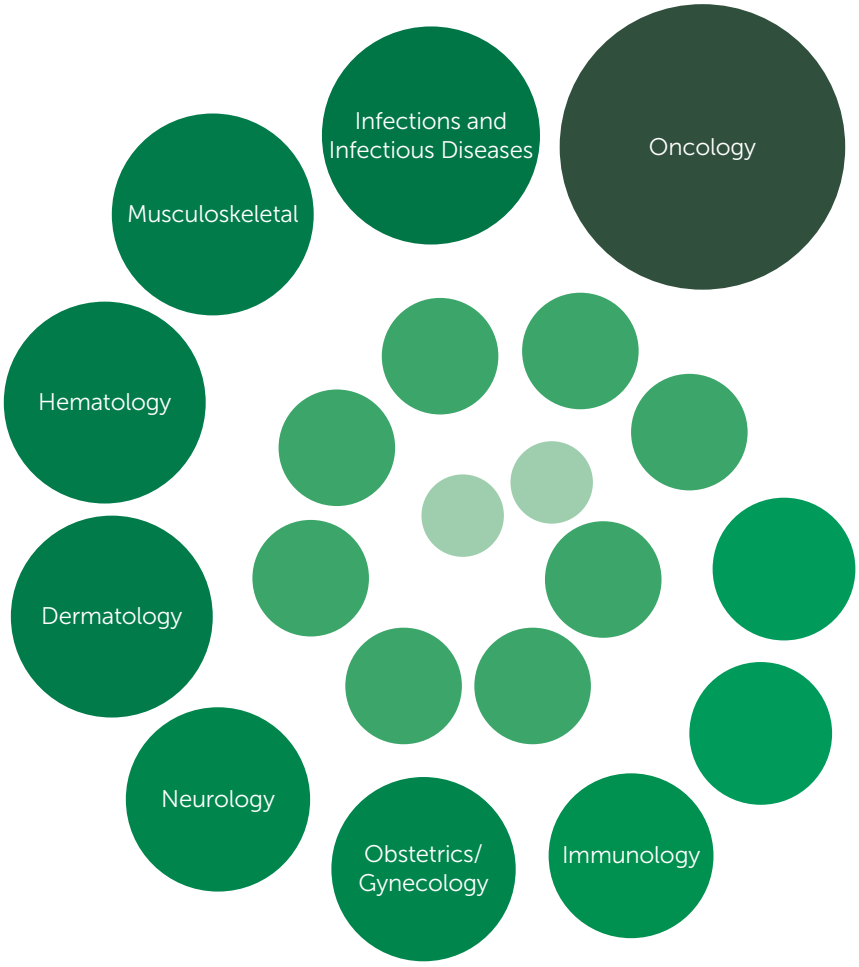
2018: Living In The Wake Of 2017

ISR reports
Smarter questions ∴ Smarter answers

With 46 new drugs approved in 2017 (51 if you include five biosimilars), we see that the pharma industry was quite busy. The number of new drug approvals more than doubled from 2016's level of 22, which begs the question: What is the knock-on effect of a near-record volume of approvals? When one thinks about the potential impact on manufacturing, market access, late-phase clinical development, and sales and marketing activities, the impact is likely substantial.

33 SMALL MOLECULES:

13 BIOLOGICS:



TOP THERAPEUTIC AREAS

- Oncology (12)
- Infections and Infectious Diseases (7)
- Musculoskeletal (6)
- Hematology (6)
- Dermatology (6)
- Neurology (5)
- Obstetrics/Gynecology (5)
- Immunology (4)
- Gastroenterology (3)
- Opthalmology (3)
- Genetic Disease (2)
- Rheumatology (2)
- Endocrinology (2)
- Hepatology (2)
- Family Medicine (2)
- Cardiovascular (2)
- Pediatrics/Neonatology (2)
- Urology (2)
- Pulmonology (1)
- Nephrology (1)

"In some instances, if there is no product launch, you will not do many studies or many promotional material reviews because you don't have a new product to be launched for the succeeding year. **But if you do have a product launch, then you have to increase your budget. That's the main reason for the increases in most instances.**"

ISR'S MARKET RESEARCH REPORT:
BENCHMARKING THE PHARMA INDUSTRY'S MEDICAL AFFAIRS FUNCTION

When Treatment For A Rare Disease Is On The Horizon, **Hope Rises — And So Does Doubt**

JOY ALDRICH

"There is nothing I can do for you. There is no treatment or cure."

That's what a neurologist told us when he diagnosed my mother, brother, and me with Charcot-Marie-Tooth (CMT), a hereditary neuromuscular disease that would progressively get worse as we got older. I was 14 at the time, and my mom was already having trouble getting up and down stairs and with daily tasks such as using a knife, buttoning a shirt, and turning a key to open a door.

CMT is considered rare; it is estimated to affect one in 2,500 people in the U.S. There are several types of CMT, categorized by the type of damage done to the peripheral nerve, but my type, CMT1A, is the most common. Basically, I have a duplication of a gene (PMP22) which is producing too much of a protein, and the result is damage to the myelin sheath that protects the nerves that conduct signals from my brain to my arms, hands, legs, and feet.

Knowing all of this, and being told that there was nothing anybody could do to treat or cure CMT, I went about my life. I filed away newsletters I received from patient groups because they seemed too depressing, but something told me that I might need to refer to them one day.

After I turned 40, I slowly started to notice changes. I struggled to walk up the stairs. Soon, I couldn't do even two stairs without a railing. I was no longer able to walk heel to toe because those muscles were atrophied, so I started walking like a stork, lifting my knee up high enough to get my feet to clear the ground without tripping. Eventually I went back to those newsletters to seek information on leg braces to help me walk with improved balance and endurance. I also was determined to turn my depression over my lost mobility into advocacy to fight for treatments and a cure.

In 2015 I attended the annual Peripheral Nerve Society meeting and learned that, although I'd been told there were no treatments to help me, there were scientists all over the world working on a cure for CMT! They were working on definitive measurements — biomarkers and clinical endpoints — to one day soon prove that treatments were working. I was thrilled!

More recently I learned that a French pharmaceutical company, Pharnext, is reporting positive results in a Phase 3 clinical trial of its PLEOtherapy drug, PXT3003, for CMT1A. It has been demonstrating not only fewer declines in patient symptoms, but improvements, too. So, if it's approved, I may even be able to regain some function! It seems too good to be true.

But my mind is whirling with questions, too. How much will it cost? Will insurance cover it? Are there any side effects? What if it doesn't work for me?

Maybe I'm afraid that it is too good to be true. I've become used to the idea that there is nothing anyone can do to stop this disease. I watched my mom go from very active, to limited mobility, to a wheelchair, to death by respiratory failure secondary to CMT, in 30 years. I'm haunted by the shadow her life is casting over mine, but still I'm excited about the hope on the horizon as I eagerly await the Phase 3 clinical trial results.

JOY ALDRICH of Seattle, WA, joined Hereditary Neuropathy Foundation (HNF) as its advocacy director to focus on the growth of HNF's online support resources for CMT patients and caregivers and to advocate for patient recruitment in clinical trials through Global Registry for Inherited Neuropathies (GRIN), a patient clinical registry.

Putting **Patients First**

SURESH KUMAR

As I turn the page on 2017, I cannot help but reflect on a remarkable, yet vexing, journey through my years in healthcare. Much has been achieved, so much more needs to be done, and yet we have not marshalled or deployed all the resources available to us.

I vividly remember an early boss disagreeing with the cacophony of competitor names that emerged as the response to his question, "Who is our enemy?" He continued, "Our enemy is not competition, it is disease." To combat disease, we have more medicines today than ever before, over 7,000 medicines are in development globally, and almost 1,000 of these are biologics. Between 1950 and 2000, lifespan increased from 48 to over 70 years, and in the last decade alone, lifespan in the developed world increased from 74.26 years to 76 years. Why then is our industry vilified? What are we not doing, or doing, to garner criticism?

> *"Few programs embrace the voice of the patient, and fewer companies leverage technology to improve patient outcomes in real time."*

I will share my perspectives of reality and facts, raise questions, and paint a picture of the emerging future. These are my observations and opinions, not those of this publication or institutions I have been associated with in the past or at present.

As healthcare policies got more complex, our industry spoke in parables, platitudes, and paradigms. Plain talk vanished. For the last five years, we have spoken about four things that will fundamentally transform healthcare:

- Patient-centricity: New positions have been created and without clarity of purpose; patients have seen little change and scant benefit
- Real-world evidence (RWE): This is a panacea constrained by fear of the unknown, by what may lurk in the shadows as adverse events.
- Moving from fee for service (FFS) to fee for value (FFV) or outcomes: Despite some progress last year, few programs exist at scale, and lack of transparency across the supply chain precludes risk sharing.
- Going beyond the pill: This is fashionable talk, but has little to show for it.

Unquestionable creativity in drug development clashes with unimaginative ways to reach and care for the patient. Impressive technological strides in biologic medicines contrast starkly with archaic commercialization and market-access practices. While patients and consumers are connected and networked as never before, our embrace of technology lags behind most other industries and would have remained dormant but for the government-led push to adopt EHR and EMR. We have progressed well in our quest to combat disease as the enemy, but we have yet to demonstrate the ability to put patients first. Few programs embrace the voice of the patient, and fewer companies leverage technology to improve patient outcomes in real time, not just as a statistic in clinical trials.

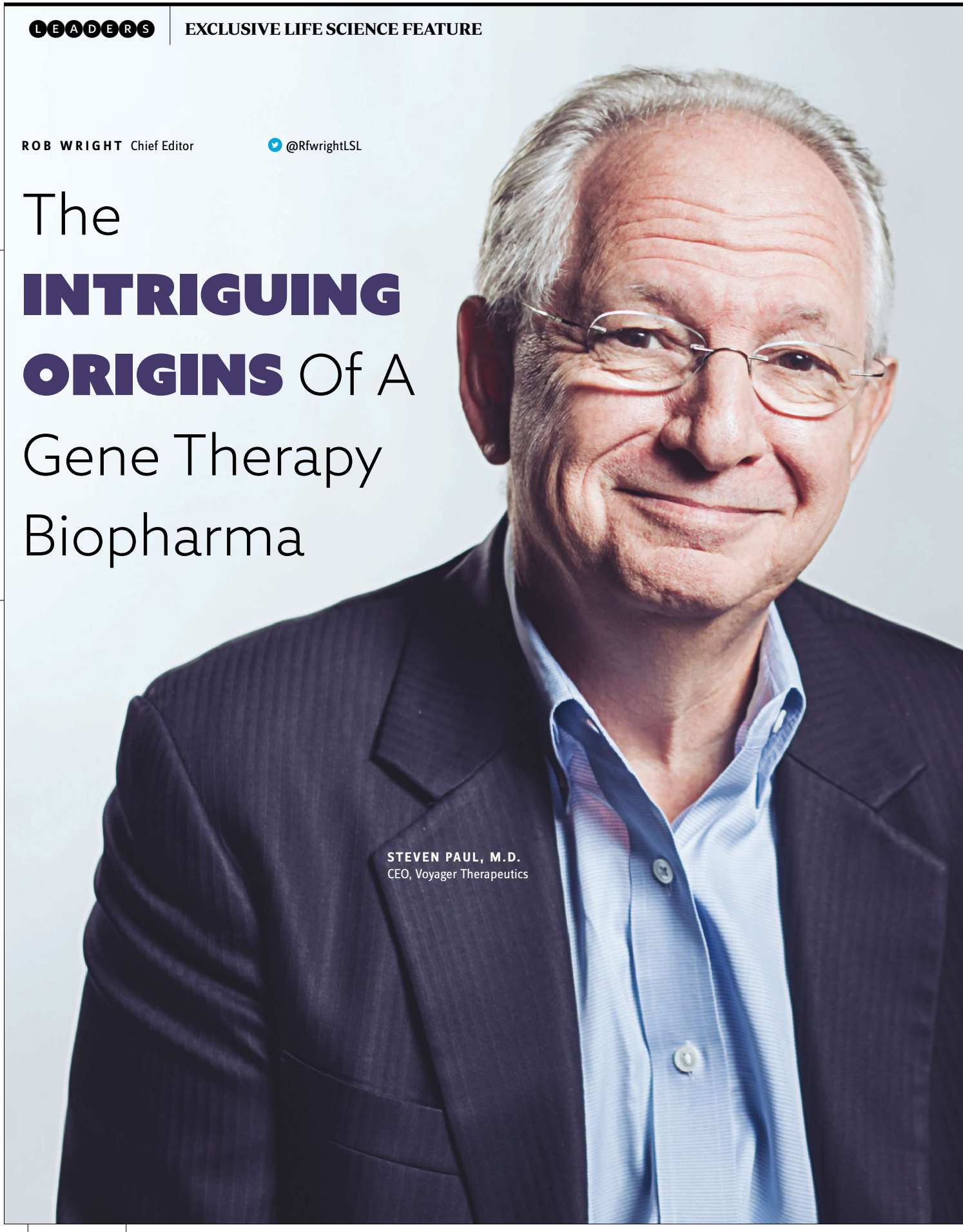
Healthcare will likely evolve from a pill or an injection to a service. Holistically caring for a patient will mean, for example, not just managing a disease such as diabetes, but caring for diabetic patients, over 80 percent of whom have at least two co-morbidities. Technology will enable us to engage patients in their care and with their consent, monitoring adherence and outcome to deliver real-time interventions via members in the patient's care continuum. In essence, healthcare will be a patient-centric service where the patient is "heard," monitored, and counseled via appropriate medical interventions while RWE is being generated. This is how patient outcomes will be improved.

Succeeding in the future will require going beyond combating disease to putting patients first. It will require pharma companies to embrace technology and transparency today.

SURESH KUMAR serves on the board of Jubilant Pharmaceuticals and Medocity. Formerly, he was U.S. Assistant Secretary of Commerce and Executive VP at Sanofi.

ROB WRIGHT Chief Editor @RfwrightLSL

The INTRIGUING ORIGINS Of A Gene Therapy Biopharma



STEVEN PAUL, M.D.
CEO, Voyager Therapeutics

The first few years of a company's history are usually filled with some unusual — and intriguing — milestones. Voyager Therapeutics is no exception.

Founded in February 2014, the company took the difficult path of pursuing treatments for debilitating diseases such as ALS and Parkinson's. It planned to do so with science rooted in the burgeoning field of gene therapy. Again, not a common or easy choice. But Voyager's science looked so promising early on that Third Rock Ventures, a VC firm focusing on biotech startups, not only invested $45 million to get the company up and running, but even provided an interim CEO in the form of industry heavyweight Mark Levin, cofounder of Third Rock, who had 30+ years of experience launching and building biopharmas.

Intriguing.

It didn't stop there, though. About a year later, another Third Rock executive, Steven Paul, M.D., took over as CEO. Paul brought more than 35 years of neuroscience expertise and an extensive track record in CNS drug discovery and development, specifically as president of Lilly Research Laboratories. On Nov. 11, 2015, Voyager achieved one of those early milestones when it raised $70 million via an IPO.

So, over $115 million raised and two high-profile CEOs from one of the hottest VC firms around, all in less than two years? I was definitely intrigued, so I reached out to Paul to find out more.

THE PROCESS OF FOUNDING VOYAGER THERAPEUTICS

"I think gene therapy's time has come," Paul says matter-of-factly after I ask why he would step away from his advisory role to lead Voyager full time. That prediction about gene therapy, he explains, is based on three years of research by Third Rock during which they spoke with dozens of gene therapy scientific experts. "We're primarily interested in investing in highly innovative companies, and we wanted to explore whether or not gene therapy was the right kind of investment for our firm."

Part of that exploration involved Third Rock holding a minisymposium where they invited a number of the leading experts in AAV (adeno-associated virus) gene therapy. During the meeting, it became clear that developing a company around AAV gene therapy was an intriguing opportunity, and so Third Rock set out to find people who could serve as founders. "We wanted not only gene therapy experts, but also the leading scientific KOLs, and we ended up pulling together a very strong team," he explains. That team consisted of the following four founders:

- **KRYSTOF BANKIEWICZ, M.D., PH.D.** — Kinetics Foundation Chair in Translational Research and Professor in Residence of Neurological Surgery and Neurology, University of California at San Francisco (UCSF)
- **GUANGPING GAO, PH.D.** — Director, University of Massachusetts Medical School (UMMS) Gene Therapy Center & Vector Core; Scientific Director, UMMS-China Program Office; Professor of Molecular Genetics and Microbiology, UMMS
- **MARK KAY, M.D., PH.D.** — Dennis Farrey Family Professor, Head, Division of Human Gene Therapy, Departments of Pediatrics and Genetics, Stanford University School of Medicine
- **PHILLIP ZAMORE, PH.D.** — Howard Hughes Medical Institute Investigator; Gretchen Stone Cook Chair of Biomedical Sciences, Professor of Biochemistry and Molecular Pharmacology, and Chair of the RNA Therapeutics Institute, University of Massachusetts Medical School (UMMS)

According to Paul, the founders made many seminal contributions to Voyager. "They provided expertise on AAV biology, gene-silencing artificial microRNA cassette technology, and many of the viral capsids for delivering genes into the central nervous system." They also helped determine what diseases were ripe for gene therapy. "Krystof Bankiewicz had done some very nice academic studies on Parkinson's disease at UCSF," Paul notes. "We liked the data generated and felt we could optimize, in particular, the delivery and dose of the gene therapy vector Krys [Bankiewicz] was delivering." (Voyager's lead program, VY-AADC for advanced Parkinson's disease, is in a Phase 1B study, and the company anticipates beginning a pivotal Phase 2/3 program and dosing the first patient during the second quarter of 2018.)

After assembling this group, Third Rock spent well over a year determining the elements for what a successful gene therapy company would look like. "In our case, we wanted to engineer these AAV vectors, because we knew the first generation of vectors, while good enough to get Voyager up and running as a company, were probably not going to be the be-all and end-all for delivering genes to the brain and spinal cord," he states. "In fact, we've come up with and in-licensed some extraordinary new AAV capsids that can deliver genes to the brain and spinal cord much more efficiently than the first-generation capsids."

TO INSOURCE OR OUTSOURCE?

One of the next things they had to do was decide how best to manufacture their viral vectors. "Unlike monoclonal antibodies and small molecules, it's not easy to find a CMO that can produce the type of gene therapies being developed at Voyager," says Paul. As a result, in the early days the company was intent on developing its own in-house capabilities to produce and manufacture its AAV vectors, not only for research studies in animals, but in human clinical trials, as well. That decision would change, though, over time. "We decided that owning our own commercial manufacturing facility would not be the most efficient use of capital," Paul explains. Instead, the plan was to own the process and export it to select CMOs, a plan still in use today.

"For us, the CMO selection process began by involving some of our internal technical experts familiar with Voyager's production process platform," Paul relates. "Then we met with multiple CMOs starting to get involved in viral vector manufacturing." Some of those had been in the field of gene therapy, but not many had been involved in AAV. A lot of the AAV work had been done in academic settings, such as Children's Hospital of Philadelphia (CHOP) and Nationwide Children's Hospital in Columbus, OH. "These facilities had very strong AAV gene therapy programs and, as a consequence, had developed their own manufacturing capabilities." Though high quality, Paul believes these centers probably could not get to commercial-grade very easily and might not even want to. "We use a very scalable process that was perfected by one of our founding scientists involving the

A PRIMER ON GENE THERAPY

We asked Steven Paul, M.D., CEO of Voyager, for a brief overview on gene therapy (for not all of us can claim to be scientists). "Gene therapy is a broad term to describe the delivery of genetic material (i.e., DNA, RNA) to correct the actual genetic mutations or defects that cause a given disease," he begins. "Based on over 25 years of research greatly facilitated by DNA sequencing and the study of genetics, we now know the genetic etiology of a large number of diseases." These diseases are primarily monogenic – disorders caused by a mutation in a single gene – and passed from parents to offspring. In the area of neurological disorders, there's a whole host of diseases where the genes have been identified as well as the exact changes in the base pairs of DNA that cause the genetic mutation. "In many cases we know the exact cellular or biological consequences of these mutations," Paul says. In Parkinson's disease, for example, there is a progressive loss of dopamine neurons in the brain, with early symptoms being shaking, rigidity, slowness of movement, and difficulty with walking.

On the other end of the spectrum there are certain gene mutations that cause a "toxic gain" of function. "Here it's not the loss of the protein causing the disease, but the mutation causes the protein to change or become misfolded, turning it toxic to the cell itself," he clarifies. This is the case in Huntington's disease, as well as in many forms of ALS. "In this type of situation, Voyager is attempting to deliver a vector that silences the gene," Paul notes. This process is known as RNA interference (RNAi). "It's literally a piece of DNA that encodes an antisense RNA molecule, preventing the expression of the messenger RNA for that particular protein and, in essence, knocks that protein down (i.e., silences the gene)," he states. Based on animal models and human genetics, Voyager researchers believe such an approach could markedly reduce progression and, if given early enough, possibly even prevent disease onset.

Paul attributes the current level of excitement surrounding cell and gene therapy as primarily being driven by two factors. "Since the human genome was first sequenced, the field has benefited from new and more powerful DNA sequencing tools that have allowed us to better identify mutations, which has greatly improved our understanding of the genetics of monogenic as well as polygenic diseases," he says. "The other major advancement, in terms of in vivo gene therapy, has been the realization that certain viruses, such as the adeno-associated virus (AAV) capsids, can be engineered to safely deliver genes to a variety of tissues, including the brain and spinal cord as we are pursuing at Voyager."

VOYAGER'S VIRAL VECTOR FOCUS

At Voyager Therapeutics, the focus for deploying its gene therapy technology always has been on CNS diseases affecting the brain and spinal cord – and diseases where there are currently few, if any, treatments. "Take ALS for example," Steven Paul, M.D., CEO of Voyager, states. "Though there is a small molecule drug that extends life by about two months, there is no truly effective treatment that slows down disease progression, and certainly nothing curative." Unfortunately, the same can be said for Huntington's disease, Friedreich's ataxia, Alzheimer's disease, and frontotemporal dementia (FTD), despite researchers possessing a pretty good understanding of the genetic underpinnings of these diseases. "Voyager started focusing on CNS disorders for a number of reasons," Paul explains. "We like the genetics. We understand the targets we're going after, and, in our view, these targets are highly validated." This reduces attrition and increases the probability that these drugs are likely to work when moved into the clinic.

So why are Voyager's AAV vectors different? "When our AAV capsids are injected, they get into the nucleus of the cell where the chromosomes and DNA are located," Paul states. "But AAV vectors don't readily integrate into the DNA of the host cell." This is different from other viruses, such as lentivirus, for example, which, when it gets into the nucleus of the cell, can integrate into the host cell DNA, he explains. "Any time a virus integrates itself into the host genome, there's a risk of causing mutations that can lead to cancer, and this is why lentiviral vectors aren't commonly used much in vivo anymore."

While AAV viral vectors do not readily integrate into the DNA, they do have a disadvantage. When a cell divides into two, the DNA that's in the AAV vector of the parental cell isn't passed on to the daughter cell. As a result, if working in an area where very active cellular proliferation takes place, the effects of the AAV virus will get diluted out over time as new cells won't contain the viral vector that had been delivered. But nerve cells (i.e., neurons) for the most part don't divide, because they are terminally differentiated (i.e., postmitotic). "When Voyager delivers a gene using AAV viral vectors to nerve cells, as in the case of our Parkinson's program, the expression of the gene being delivered is very durable, on the order of many years or perhaps even decades," he attests. "In monkey studies for our Parkinson's program, researchers have delivered a gene that encodes a therapeutic protein allowing for levodopa (L-DOPA), the medicine used to treat Parkinson's patients, to be converted to the neurotransmitter dopamine, which is what is deficient in the brains of these patients." According to Paul, there are many years of monkey data, and over four years of human data, indicating no loss of the delivered gene. Not long ago a research group in Japan reported 15 years' worth of monkey data with no loss of the delivered protein. "This is why we believe our approach has the potential to be a very long-term fix via a one-time treatment," Voyager's CEO affirms.

use of baculovirus Sf-9 insect cells," he states. As such, the company wanted to have close contact with any CMO selected so that internal production team could clearly communicate its process.

Mass Biologics' relative close proximity to Voyager was one of the primary drivers behind it being selected. Good timing also played a role in this decision, as the CMO had recently opened a new manufacturing facility in Fall River, MA. "This afforded us an opportunity to collaboratively build the internal facility with the bioreactors and layout we desired," Paul shares. Since then, Voyager has initiated its first cGMP production campaign for viral vectors for its Parkinson's program. "We have produced a number of GLP lots of this vector at 200-liter scale and are in the midst of developing the GMP vector for the pivotal trials for our Parkinson's study," notes Paul.

MORE INTEREST = MORE OPTIONS FOR GENE THERAPY MANUFACTURING

While Voyager feels good about where it is presently regarding manufacturing, it has been exploring other potential CMOs to work with for its commercial vector program. "We anticipate using the same fundamental process we have developed thus far with Mass Biologics," he says. "But since we first started Voyager, a lot more CMOs have become interested in the field of gene therapy."

However, according to Paul, there is something as or even more important than choosing the right CMO for its future commercial business. "We think what's important is investing in process R&D (i.e., improvements made over time to the Voyager manufacturing process) to make it as efficient and scalable as possible," he says.

"Many processes, whether for insulins, antibodies, or small molecules, need to improve and become more efficient over time, and that's what we're doing right now with our gene therapy manufacturing process." In other words, no matter what CMO Voyager selects for commercial manufacturing, it is incumbent to first have a well-defined and efficient production and manufacturing process and to be able to effectively communicate this process and work closely with a CMO, if it expects a CMO to be able to execute its plans.

DENVER LOUGH
Chairman, President, CEO, & CSO
PolarityTE

THE ENTERPRISERS

Life Science Leadership In Action

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

PolarityTE: Beyond Cells, To Whole Tissue

PUBLIC COMPANY (Nasdaq: COOL)

MARKET CAP: $139.5
(as of close on Dec. 29, 2017)

CASH: $3M at Sept. 12, 2017

STARTUP DATE: Dec. 8, 2016

NUMBER OF EMPLOYEES: 31

FOCUS: Regenerating lost tissues
in their original complex forms

If you want to be a real enterpriser, try bringing a new solution into a troubled space. PolarityTE gave itself the challenge of entering the race to regenerate skin and other tissues, a field littered with failures piled up for decades. The problem? "You can put stem cells in a petri dish and surround them with growth factors, but all you get is a mass of useless cells," says Denver Lough, chairman, president, CEO, and CSO of the company. "Or, if you put the cultured cells into a wound, you only end up with scar tissue."

Lough and his cofounders began their journey to enterprise in the trenches of actual patient treatment — cleaning up, dressing, and "smelling" the wounds caused by fire, chronic bedsores, and a myriad of other insults. As a group of plastic surgeons at Johns Hopkins University, they saw the destruction firsthand, as well as what they considered the pitiful failures of "artificial skin" products of the time. Besides simple compassion, their work required an intimate understanding of the composition, structure, and regenerative potential of living tissues such as skin or bone. The experience drove them on, in both motivation and informed design, to build a better way of restoring fully functional tissue.

"We left Johns Hopkins because we were tired of people telling us, 'Here's this incredibly novel product that's only $40,000 a square centimeter. You can put it on your patients, and you will regenerate something.' But all you get is scar tissue — the same thing, over and over and over again," Lough recalls.

"Regenerative medicine cannot take form or operate in isolation," Lough says. "Most regenerative-medicine companies are focused on making a single silver bullet to regenerate living tissue — a single stem-cell type, growth factor, drug, or polymeric scaffold. If that were possible, why have so many companies failed to do it? Polarity embodies the fact that there is no single agent or combination of agents that can make regenerative medicine work. Tissues have polarity — up, down, backward, forward, left, and right. They operate together and touch each other, connect to an extracellular matrix and blood vessels, and rely on gradients of growth factors. All of those elements together guide the development of stem cells to replace lost tissue."

Skin is the lead product for PolarityTE, with a planned launch tethered to further clinical research in selected institutions, but it is also developing others and aims to apply its platform widely over time. Current programs include replacement products for bone, vascular, muscle, cartilage, nerve, and fat, with more areas considered for the future.

JUMP START

Creation of the basic technology for producing the tissue replacements began several years ago, but the company did not begin to form until late 2016. All of the principals had conducted discovery research in tissue regeneration and wanted to see their techniques and inventions go beyond academic science — to overturn the status quo in patient treatment. Only a business enterprise could hope to achieve that goal. Funding was especially tough from the get-go because the founders wanted to be the ones steering the company, not the funders. They already had rejected several offers from half a dozen VCs who sought control of the company in exchange. The company's academic origins may have raised a red flag with investors, but it was actually the founders' rejection of academic restraints that put them on a business path.

"My wish had always been to continue working at Johns Hopkins as a burn director," Lough recalls. "I wanted to grow skin for burn patients and contribute all types of tissue substrate to other fields at Hopkins, such as orthopedics and neurosurgery. But we realized there was no way for that to become reality because of the bureaucracy associated with academia. Academia wants to get its hands involved with everything because it wants to make a name for the university."

Venture capital presented a similar problem, in Lough's view: "If you take away management from us, you take away the passion, you take away the innovators, you take away the leaders, you take away the people in the trenches, and it suddenly becomes all about product, margin, and profit. That leads to failure."

Enter the angel.

Dr. Philip Frost, the well-known multibillionaire investor in Miami, approached the company, offering to

take it public and give it cash up front — as long as the founders retained the management responsibility. *(Editor's note: Frost had been investigating the regenerative medicine field, and in doing so, he had read the founders' published papers on the subject.)* Lough relates Frost's message: "If you believe in your technology, your cause, your network, and your ability to get this to market, be public. Put it on the table. Prove it to me." As chronicled elsewhere, the plan was ingenious if a bit anachronistic. The company would merge with a struggling computer-gaming business, Majesco Entertainment, to acquire its assets and Nasdaq listing (COOL), and at the same time assume the name PolarityTE.

What's the TE stand for? "That's a great question; everyone always wants to know that," says Lough. "Most assume it means tissue engineering. It is not tissue engineering, but it is in the mission statement that drives the company every day. If you want to know what it is, you have to come work for us! A clue: we don't care about what people know, but we do care about how they learn and how they drive themselves forward."

Before Frost came into the picture, Lough's encounters with life science investors sparked some thoughts about key differences between "dry" high tech such as IT and the "wet" high tech of life sciences. "Biopharma takes so much money to get off the ground, and in addition, you run into all these barriers based on the current central dogma. You must make sure you fit the algorithm the oncologists want or the way regenerative medicine has been taught. But if you look at the people who founded and drove the largest high tech companies today, they are all people who defied the accepted ways."

Lough believes the next few years will bring a tremendous shift in biopharma development, especially in regenerative medicine — from venture capitalists running virtual companies, to more "garage-based," do-it-yourself enterprises. He trusts the result will be more innovation at lower cost. "It's time for companies that bring real technology forward as inexpensively as they possibly can and get it to patients as quickly as they can. That will become a paradigm shift in the way biopharma and regenerative medicine truly develops."

SUPPORT STRUCTURE

Once launched, PolarityTE composed itself and its technology with a surgeon's perspective — focusing beyond the single-agent regenerative model to one of multicomponent support. Lough likens the company's approach to keeping a patient in a familiar home environment with all the elements needed for treatment provided there — "offering all of the supportive components, from interfaces, to growth factors and the extracellular matrix, all integrated into the system, and processed slightly to allow it to propagate and regenerate full thickness of skin, hair, or other tissue, with all of the necessary layers." The platform can thus cross over into regenerating viable tissue in a variety of organ systems.

> If you take away management from us, you take away the passion … and it suddenly becomes all about product, margin, and profit. That leads to failure.
>
> **DENVER LOUGH**
> Chairman, President, CEO, & CSO
> PolarityTE

The platform creates an infusible product consisting of a minimally polarized functional unit (MPFU). In the MPFU, stem cells taken from the patient are surrounded by extracellular structures in a matrix containing growth factors, mimicking natural conditions of healing in the body. That includes the aforementioned polarity of tissues arranged in ordered layers and forms that serve as substrates for other layers and forms. SkinTE reflects the polarity of natural skin, with all of those components arranged in the same order.

The resulting product is "autologous," meaning it consists of the patient's own cells, and "homologous," specific to the tissue to be regenerated. It comes in a form with an almost paste or oatmeal-like consistency inside a needleless syringe for deployment and application diffusely across the open wound. With polarity intact in the implanted product, the cells and tissue are capable of self-orientation through migration into the proper layers. Over a short period of time, the regenerating skin fully aligns into its natural layers through cell migration to the appropriate location.

Lough says the company designed the product to be administered almost anywhere, even in remote, undeveloped areas of the world. From each patient, using simple tools and instructions supplied by PolarityTE in a "Harvest Box," physicians harvest a piece of full-thickness skin, then send the sample back to the company in a FedEx UN 3373 shipment for processing into the MPFU, using the supplied carton containing a NanoCool chemical cooling

REGENERATIVE REVOLUTIONARY

PolarityTE takes a strong stand on regenerative medicine – it must mirror the complexity of actual living tissue. The company's CEO, Denver Lough, puts its technology for regrowing the patient's own skin, bone, or other tissue into the perspective of rapidly advancing science. He also issues a challenge to the field's status quo.

LOUGH: If you take the tissue and introduce a variable such as a new gene or new type of growth factor, you only measure the outcome you're looking for. But what about all the things you're unaware of? We didn't know really what the field of metabolomics was 10 or 15 years ago. We didn't know what micro RNA, single hairpin loop RNA, or dicer was. Then the field began to realize, we're affecting things we don't even understand. But the greatest discoveries of humankind all come from the realization of reality. Someone just realized this is the way the natural system works, this is the way it works. The greatest discovery in the world was probably gravity, but it just took time for people to actually understand what it really was. Our company's technology embodies the same idea, saying, "Look, there are natural biologically sound mechanisms for the way hair follicles regenerate." If we apply those same mechanisms, play around with the tissue just slightly to make it easy for people to deploy, then we can actually give it to people to regenerate full-thickness, organized skin, as well as organized bone, cartilage, muscle, liver. We don't believe a single drug can do that. Of course, people love off-the-shelf products; you can have a huge margin on them, you can profit well. The problem is, in regenerative medicine, they didn't really contribute anything, so they play these little marginal games with each other, saying, "My product is slightly better." We're saying, the heck with that. We need to change the paradigm – the way regenerative medicine has been propagated throughout society.

agent. A smartphone app gives all caregivers involved instant, 24-hour access to a real human being at the company providing expert assistance. After the patient sample arrives, the company processes it and returns the product within 24 to 48 hours to the practitioner.

> Funding was especially tough from the get-go because the founders wanted to be the ones steering the company, not the funders.

"People say it sounds too good to be true," says Lough, "But the only assumption we ever ask them to make is your own skin can regenerate your skin." He says SkinTE can generate full thickness skin, with hair follicles, epidermis, dermis, hypodermis, blood vessels, and appendages such as sweat glands and sebaceous glands. Touting single-agent solutions for regenerating skin, he maintains, is tantamount to claiming the ability to circumvent biology, evolution, and the immune system. Aiming to cover all the bases of tissue complexity, PolarityTE even went beyond the founders' own deep knowledge of wounds and healing, bringing in 40 clinical advisors from numerous medical institutions to guide its technology design.

"We want to have the best product for regenerative medicine, hands down. Absolute best," he says. "But at the same time, we want to provide it to everyone we possibly can for the most cost-effective price out there, so we can pass on the savings to the healthcare industry, and to payers, providers, and patients. We want it to be used not only by specialists, but also by nurse practitioners and physician assistants."

Assuming the always big "if" of whether the technology works as planned, it could limit ER visits, hospital stays, and use of antibiotics — and the ill effects of the same. "You dress it as you would a typical skin graft, and you let it heal," Lough says. "We're not reinventing the way that dressings or skin grafts are done." He draws a sharp contrast between the simple procedure just described and a logistically complex cellular therapy such as CAR-T. Thus, although his company's product is a more comprehensive assembly of cell types than single-agent therapies, it is uncomplicated in administration.

Unlike drugs, human tissue products such as SkinTE do not go through three-phase clinical trials but have a much shorter potential path to market. Companies must register such products with FDA's CBER (Center for Biologics Evaluation and Research), which mainly focuses on purity, safety, and one other subject that PolarityTE largely avoids: preventing the spread of com-

municable disease. The company achieved FDA registration of SkinTE in August 2017 and is doing a limited release of the product in a selection of large clinics as it scales up manufacturing and distribution capacity. Human clinical data will emerge from the early adopters.

Perhaps the preceding description seems all too simple, and of course it is. Offering a new product is one thing; winning adoption by all of the interested parties — the usual "p" chorus of patients, physicians, and payers — is quite another. In meeting that challenge, PolarityTE's team of founders and advisors may have the advantage of coming full circle, from actual practice in the market, to product development, and back into the market with a technology they have designed for that setting. Maybe that is why the company chose an especially challenging objective in a pilot study for SkinTE — burns.

That was no accident. Lough's team knew the stark reality and high stakes of treating burn patients, and not just from general experience. A specific, dramatic situation educated them indelibly.

EXPERIENCE FORMS

In 2014, at a dance party in an empty swimming pool in Taiwan, 512 people were burned when a festive starch-based flour lit on fire and exploded. President Ma of Taiwan called Dr. Stephen Milner, now the company's chief clinical officer and then director of the burn center at Johns Hopkins, asking him to bring his team to Taiwan to help triage and treat the burn patients. Having read their published papers on healing burns, Ma also asked whether the team could regenerate patients' skin.

"At that time, the company wasn't real, it was just a concept, but right then and there I realized, as a physician at Hopkins, I had reached a terminal velocity," says Lough. "I could only treat one patient at a time, I could only put one stitch in every 10 seconds, I could only see so many patients in a clinic. I could only give this much fluid, I could only take this much skin, and so on. If I leave Hopkins, I bring a brilliant team with me that are all dedicated physicians, saying 'to heck with it, we need to change regenerative medicine.'"

Lough looks beyond skin regeneration in applying the technology to lost bone, muscle, fat, and cartilage. Pressure sores present an example of wounds that involve all of those components and more. "To anyone with a deep wound, we could give skin, fat, muscle, bone — we could even restore peripheral nerve elements to innervate components of those muscles so they do not atrophy. We could prevent the sort of protein degradation that will continue breakdown of surrounding tissues."

Press coverage of PolarityTE has mainly concentrated on the issue of academic scientist turned CEO, even though Lough and his cofounders were hardly naïve to business. But the more interesting story might be how the company marries science to actual practice, out of which its business model emerges. If its technology somehow failed, at least it would have championed practice-centered discovery and development versus the arguably oversimplified early efforts in the infant field of regenerative medicine.

Lough makes the stakes emphatically clear: "People have glorified the technology of regeneration without really recognizing how the applications must be useful to people who have been in the trenches and know the full spectrum of complications that exist in wounded tissue. Deep tissue needs to heal in a certain way. The answer isn't always just changing the dressing in a vac [i.e., vacuum therapy with vacuum-assisted closure devices]. Creating one-dimensional products like a single hairpin loop RNA for treating a pressure wound — it's unbelievably expensive, and it's never going to work in a human being."

Having lost a friend, and possibly my mother, to unhealed wounds taxing the entire body, I am allowed to hope for the success of PolarityTE in the way it projects. The company appears clear-headed enough to understand how biology can perversely defeat the most convincing logic, but one could hardly argue with its complex view of tissue regeneration. Oh, and don't worry about the academic origins of its leaders. They seem quite in touch with the real world, a primary requirement for doing business well. L

2018 Likely A Banner Year For IPOs

GAIL DUTTON Contributing Editor @GailLdutton

Based on recent financing data, 2018 is positioned to be a blockbuster year for life sciences company IPOs. 2017 third quarter VC financings were the highest in the industry's history, and investors are returning to the sector, searching for undiscovered, disruptive technologies.

"We're seeing signs of a healthier market in 2018," Wende Hutton, general partner, Canaan Partners, says. "There was a lot of uncertainty after the 2016 presidential election. Forty percent of the IPOs in Q1 2017 failed to meet their "in range" prices, and many withdrew. So far in Q4 2017, none has failed to meet their expected prices." That indicates a better match of demand and quality that meets investors' expectations, which has triggered the return of both hedge fund and general investors.

"Perhaps we won't see IPOs at the levels of 2014 and 2015, but 2018 should be a nice uptick from 2016," Hutton predicts.

NUMBER OF DEALS HOLDS STEADY, BUT ROUND SIZES INCREASE

The number of new venture capital-backed financing deals for U.S. biotechs in 2017 is comparable to the usual number of 400 to 450. With one month left in 2017, Pitchbook reported more than 470 deals. One hundred of those occurred during Q3. This implies more funding for a set number of startups, which may leave many new companies undercapitalized.

With a record for biotech venture funding of $9.3 billion midway through Q4, round size is getting larger. A handful of deals has exceeded $100 million, including Intarcia at $650 million, ADC Therapeutics at $200 million, consumer DNA company 23andMe at $250 million, and SpringWorks Therapeutics at $103 million. The average amount of funding per company (based on Q1 to Q3 2017 data), however, was closer to $26 million, with the median amount at approximately $12 million.

"A lot of the recent financings have been crossover or mezzanine fundings, which puts larger amounts of capital on companies' balance sheets," notes Bruce Booth, D. Phil, partner, Atlas Venture. The Intarcia financing, for instance, was a series EE round. This influx of capital helps companies explore more options, quickly increases their valuations, and puts them in a good position to enter the public markets in 12 months.

When all public and private financing sources are considered, funding for life sciences companies in 2017 may reach $67 billion, predicts Manuel Henriquez, founder and CEO of Hercules Capital, a large nonbank lender to VC-backed companies. "That's down from the old days, so players like us supplement with venture debt, which is more strategic." Venture debt debuted about five years ago as a royalty-based finance model in which a company sells a percentage of future revenue to generate $60 to $100 million in cash now, he explains.

RETURN OF INVESTORS PUMPS UP AVAILABLE CAPITAL

Biotech companies are benefiting from a larger than usual number of investors from outside the traditional biotech venture investors. "In most cases, these funding sources are great providers of growth capital," Booth says. Scottish investment management firm Baillie Gifford, for example, invested hundreds of millions of dollars into biotech.

Hedge funds and general investors also are rotating back into the market, after leaving in 2016, Hutton notes. "That adds more sources of funding, which implies a steady stream of IPOs in 2018."

While the money is certainly helpful, these investors are notably different from traditional biotech VCs. "Most of the large asset management firms are investor traders," Booth says. They typically have a strong desire for the company to go public. These nontraditional biotech investors tend to be more hands-off than biotech VCs, rarely taking seats on a company's governing board or sharing their business-building expertise with the enterprise. Nontraditional biotech investors also may lack the in-depth scientific expertise to evaluate specific drug development programs, leaving them susceptible to the hype around a drug development program.

> *"In 2018, we'll see more companies being opportunistic rather than waiting to hit their milestones before going out for funding."*
>
> **BRUCE BOOTH**
> D. Phil, partner, Atlas Venture

That expertise gap may have contributed to the boom and bust of Axovant stock, Henriquez suggests. "High awareness of the potential Alzheimer's blockbuster the company's developing led to a $2.5 billion market capitalization that let the company build its coffers and retain ownership. But, when Phase 3 trials showed its drug was comparable to placebo, Axovant's stock plummeted from $2.5 billion to $750 million within a few hours. Had the compound worked, Axovant would have become a $7 billion company overnight."

Alternatively, Hutton suggests, the boom and bust of the stock price could have been predicted simply because neurodegenerative drug development is a particularly high-risk endeavor.

USE THE TRENDS

Flexibility is as important in financing as it is in platform development. Rather than counting on an IPO exit, biotech companies should structure themselves and their programs in ways that let them pivot to access a variety of options. For example, Henriquez says, "Companies should have both venture debt capital and equity capital on their balance sheets as an insurance policy." This ability to access different types of capital frees them from depending on any one funding source.

"When capital markets are flush and willing to invest, take advantage of the opportunity," Booth advises. "In 2018, we'll see more companies being opportunistic rather than waiting to hit their milestones before going out for funding. Often, these firms already will be venture capital backed."

Having a variety of exit options is important, too. Hutton advises young companies to engage early with strategic buyers, such as Big Pharma. "To increase the chances of success, determine whether there is a ready palette of pharmaceutical buyers, and then test the waters." The objective is to determine what those companies need and then to develop a clinical plan going forward that meets those needs. This involves not only delivering good clinical outcomes but also all the details — including the right formulations, the right milestones, and an experienced management team — that partners and investors expect.

TALENT AND RISK ARE TODAY'S CONSTRAINTS

Capital, even for early-stage biotech companies, won't be the main constraint in 2018. "The average size of Series A financings has increased twofold in the past 18 months," Hutton says. At the same time, "VC rounds are becoming significant for fewer players." For VCs, pulling together the teams needed to advance exciting science is expensive, so the rounds get larger.

That means that management talent and an appetite for risk are today's bottlenecks. Biotech entrepreneurs are different from those of other industries, and that difference exacts a price. While the IT industry, for example, is fueled by innovators in their mid-twenties, most of the biotech entrepreneurs are in their mid-forties and fifties and have a history of accomplishment in science and drug development. "You need people who are skilled in the art of R&D, and most biotech entrepreneurs learned that by working in Big Pharma and other biotechs," Booth points out.

2018: YEAR OF THE IPO OR YEAR OF THE DOWN ROUND?

After years of exits through Big Pharma partnerships and acquisitions, the biotech industry can expect 2018 to be a promising year for traditional IPO exits. An increasingly business-friendly climate in the U.S. is leaving investors optimistic. Stock markets have hit all-time highs, and, as 2017 financings indicate, investors are flush with cash. As that money flows throughout the industry, it is jimmying open the IPO window.

The only risk is whether the ready cash will lead to overvaluation and an eventual downturn, like the ones that followed previous booms. Booth admits it's possible. "In general, as companies raise more money, their valuations rise. If capital markets tighten while companies' valuations are incredibly high, those companies risk experiencing a down round. They may go public at prices that are lower than their last rounds of funding, or see their valuations are lowered. It's a basic market cycle." L

How To Survive The Perilous **Life Sciences Startup Climb**

JENNIFER RINGLER Contributing Writer @JenniferRingler

Flagship Pioneering in Cambridge, MA helps life sciences startups come to fruition, but you'd be wrong to call it a venture capital firm. Instead, the company focuses on innovating, forming, and growing new companies in the life sciences using its own funding, all within its own organization; it doesn't offer capital to external startups or look at business plans.

"From day one, our intent was to innovate and create new companies," says Noubar Afeyan, founder and CEO. With that intent, the company began in 2000 with a handful of new projects that gradually became startups, and as those companies started to grow bigger, Flagship added more and more. "It's a bit like starting a new vineyard," says Afeyan. "For the first couple of years you're still cultivating the original crop, and it needs to grow, and the growth becomes cyclical, rather than beginning from a dead start and being at capacity."

After that, the company dabbled for a few years in investing in outside projects, but for the past seven years, it's been focused on developing its own companies through VentureLabs, its innovation arm.

COVERING UNCHARTED TERRITORY

There are significant differences between the way most life sciences companies innovate and the way Flagship does it, according to Afeyan. For bigger, already-established companies, he says, the inspiration for new drugs comes from what he calls "adjacencies." Meaning that a company will look at an area in which it is already a leader — cardiology or asthma, for example — and iterate from there. They might come up with a new drug for another cardiac indication or test their asthma drug for efficacy in treating seasonal allergies. "By expanding from their core, large companies produce a lot of value. They can estimate which direction will have the most or least risk and be most or least lucrative and decide from among many different adjacencies which ones to focus on with their resources." But startups don't have the luxury of past successes — or capital — as a springboard.

Flagship's team of 75 staff members — more than half of whom are M.D.s or Ph.D.s — instead starts from scratch, working from scientific theory up, "well beyond any zone of adjacency," according to Afeyan. The company's "hypothesis-driven innovation" method is a four-phased approach, "very much based on the notion that disruptive, unexpected innovations aren't made by people with goals and objectives," Afeyan says.

HAVING THE RIGHT TOOLS

Phase 1 — Hypothesis Generation: The team first works to come up with entirely new ideas/solutions in the life sciences industry, not basing its hypotheses on existing research or projects. "Instead, we imagine all the possibilities of what can be done," says Afeyan. "Then we expose our ideas to a vast network of collaborators from academia, industry, and the startup world, who in turn tell us all the ways in which our ideas are bad." The team then refines and tweaks its ideas until it has something that "Nobody can explain why it's a bad idea anymore, other than it's never been done."

Phase 2 — Feasibility Testing: Once they've got an idea that the naysayers can't pick apart any further, "We go to our own laboratories and test the scientific basis for our hypothesis," says Afeyan. "And most of the time, the second phase kills the idea. But sometimes it works and sets us up to form a new company." If the idea proves

scientifically feasible in-house, Flagship Pioneering starts forming the internal team that will be the nucleus of the new startup.

Phase 3 — Internal Venture: During this phase, the core team of the new company comes together from Flagship's internal staff, and they begin to execute product- and platform-development plans, assemble board members, and start recruiting leadership for the new company from outside the organization. The new company will stay in this phase, under the wing of Flagship Pioneering, for two to three years.

> *"Disruptive, unexpected innovations aren't made by people with goals and objectives."*
>
> **NOUBAR AFEYAN**
> Founder & CEO
> Flagship Pioneering

Phase 4 — External Venture: The new company gradually moves from Phase 3 to 4 as the external leadership team solidifies and a CEO and board of directors is ready to work independently to help the startup flourish. "Any executive who joins a startup has to be compelled by the reward-risk ratio, and this is no different," explains Afeyan. "The only difference is that our companies are being born out of a highly repeatable process that has a long track record behind it."

CLIMBING WITH EXPERTS

This approach has helped Flagship Pioneering continue to recruit top leadership to its startup ventures. In September 2017, Flagship recruited the former CEO of Cubist Pharmaceuticals, Mike Bonney, to startup Kaleido Biosciences, which focuses on developing interventions that can enhance and protect the functions of the microbiome, targeting specific disease processes and improving general health. And in October, 23-year Sanofi Genzyme veteran David Meeker signed on as CEO of another Flagship Pioneering startup, KSQ Therapeutics, which focuses on discovering the function that each human gene plays in multiple diseases and developing tailored drugs based on that information.

These are just two of the many startups that have found success through Flagship Pioneering. Since the company's founding in 2000, it has originated and fostered the development of more than 75 scientific ventures, resulting in $19 billion in aggregate value, more than 500 issued patents, and more than 50 clinical trials for novel therapeutic agents. Of the 50 ideas Flagship explores each year, Afeyan says only six to eight end up launching as startups.

Among Flagship's most successful endeavors is Moderna Therapeutics, which is developing a new class of medicines made of mRNA. "The potential implications of using mRNA as a drug are significant and far-reaching," according to Moderna's website. "It could transform not only how certain diseases are treated but also how medicines are discovered, developed, and manufactured — at a breadth, scale, and speed not common in the biopharma industry."

"When we started Moderna in 2010, there was absolutely nobody who believed that mRNA could be a drug," says Afeyan. "Today we have 10 human clinical trials all based on mRNA drugs and vaccines, in cardiovascular disease, in cancer, and in rare diseases. That's a completely unprecedented speed of developing a whole new medicinal area." In June 2016, Merck and Moderna announced a strategic collaboration to advance novel mRNA-based personalized cancer vaccines. In September 2017, Moderna announced the completion of a Phase 1 study of mRNA AZD-8601, the first-ever mRNA therapeutic to be evaluated in a clinical study, which is being developed by Moderna's partner AstraZeneca as a potential treatment for cardiovascular diseases. And most recently, in November 2017, the company announced first-in-human dosing for its Phase 1 study of mRNA-4157, a personalized cancer vaccine for the treatment of solid tumors.

REACHING THE SUMMIT

When asked what spells success for life science startups, Afeyan has a few pearls of wisdom. The first is about commitment. "People tend to think of startups in general — not just in the life sciences — as a gamble or a sort of lottery. They think they will either succeed or fail," he says. "But I think it's quite different from that. Innovation and starting new companies is a serious activity. It shouldn't be taken lightly or viewed as a game or something that is binary. It's a serious, long-term commitment, not a lottery."

Secondly, he says, "People can benefit from being thoughtful about long-term value creation. When you climb a mountain, you plan for how you'll get to base camp one, then base camp two. It's not enough to say, 'How am I going to summit this mountain?' Often, people don't think about the sequence of steps that will incrementally deliver value. As a result, they expose themselves to way too much risk by leaping for the finish instead of gradually creating value and honing their skills along the way."

How To Keep Employed In A Changing Biotech Workplace

K. JOHN MORROW JR., PH.D.

According to Dr. Sheila Connelly, our industry's plethora of mergers and acquisitions ensures one thing — job security isn't what is used to be in biopharma. Having worked for Big Pharma, academia, small biotechs, and for herself, she's been through many of the common trials associated with M&As, while at the same time, dealing with the challenges of discovering new drugs.

Eliminating highly paid directors and other top-level positions as a strategy to save money? Check. A new top executive takes over and replaces the "old regime" with their own people in order to "make their mark" on the company? Check. A small, preclinical, growth-oriented company with cutting-edge R&D struggles due to a lack of resources to carry a project into the clinic? Check. A large pharma company eliminates a whole program because it is determined not to be profitable? Check.

"It doesn't matter if you work for a big company or a small one, these kinds of changes are likely going to occur," says Connelly. "The only thing you can *really* do is stay flexible by working in a variety of ever-changing research areas — and keep networking."

Since 2014, Connelly has been VP of research at Synthetic Biologics, a late-stage clinical company focused on developing "therapeutics that preserve the microbiome to protect and restore the health of patients." (See our "Companies To Watch" article on Synthetic Biologics in our April 2014 issue.) Prior to this position, she had worked in Europe and the United States, experiencing mergers, upsizing, and downsizing.

It all started after she earned her Ph.D. at Columbia University and did her postdoc training at the Friedrich Miescher Institute in Basel, Switzerland, operated by Ciba-Geigy. She went to work for Genetic Therapy, Inc. (GTI), a pioneer in gene therapy in the early 1990s, focusing on developing gene-delivery technologies to correct genetic and acquired diseases. "I went from RNA processing in plants to gene therapy — and ended up working with my old colleagues from the Friedrich Miescher Institute. I told people that I changed companies, changed countries, and changed fields but continued researching with the same group of coworkers."

She explained her moves as a three-dimensional chess game, "GTI ended up getting acquired by Sandoz, and Sandoz and Ciba-Geigy merged to form Novartis in 1996. So, we were Novartis for a few years." But in those years, there were major setbacks in the gene therapy field. By 2003, Novartis — seemingly not interested in gene therapy anymore — closed GTI, and its technology was acquired by Cell Genesys.

EXPLORING THE ENTREPRENEURIAL LIFE

In the wake of the GTI closure, Connelly decided to start her own company, Advanced Vision Therapies, an ocular gene therapy company. With two GTI colleagues, she licensed back the IP developed at GTI, a lentiviral vector technology, and several therapeutic genes for ocular gene therapy. AVT (founded in December 2002) applied for its first SBIR (Small Business Innovation Research) grant in April 2003 and for additional grants at every subsequent submission deadline. Connelly felt they were lucky to get their first award, but after that, they came in a torrent, with the company receiving 10 SBIRs through 2006.

Still, she and her colleagues believed that AVT could not be competitive and bankroll its product through the long process of manufacturing, preclinical testing, and Phase 1 trials on grant money alone. "The progression was too slow, and we were not comfortable hiring more employees with only grant income. We were acquired by Wellstat in 2005, and the expanded company became Wellstat Ophthalmology. This allowed us to go on a hiring spree, peaking at 17 employees."

Although Connelly felt that they were now on a smooth track, this was not to be. "They didn't take our products into clinical trials as promised, so I left in 2010."

FROM A DIVESTITURE TO A COLD CALL

Next, she took a position with Intrexon, a company investigating biological solutions in areas including medicine, agriculture, nutrition, personal care, fuels, and chemicals. There she was in charge of translational research, a group of about 22 people tasked with advancing diverse projects across multiple therapeutic areas. She realized Intrexon's technologies were well suited for application to ocular gene therapy, so she advocated the creation of an ocular program. However, 14 months later, the company divested parts of the translational research program, which resulted in her exit from the company.

"The only thing you can really *do is stay flexible by working in a variety of ever-changing research areas — and keep networking."*

SHEILA CONNELLY, PH.D.
VP of research, Synthetic Biologics

In 2012, through a cold call, she landed a position as VP of research for GrayBug, a startup out of Johns Hopkins University in Baltimore. Later, she found out that one of the founders of the company was a collaborator from her previous positions at GTI and AVT. This company focuses on sustained-release drug delivery to the eye, and at the time Connelly joined, there were only five employees. The founder and CEO was looking for someone who could bring grants into the company, and Connelly was able to deliver as promised.

"But this clearly wasn't working for me. So when an old colleague from GTI called me for advice about finding someone for a position at his company, I was intrigued and said, 'I know the perfect person ... me!'"

In 2014, Connelly moved to her current position at Synthetic Biologics, in Rockville, MD. The company pursues infectious diseases with a strong focus on the gastrointestinal tract, taking advantage of the advances in the characterization of the human gut microbiome. "Once again, I moved into an area in which I had no prior experience, but since the study of the microbiome is a relatively new field, we are all learning it together. Things have been going well here; we have two products that finished Phase 2b trials."

Connelly believes she finally has found a good fit for her career goals. "What I tell people, including investors, is that this is a company where we are on the cusp of producing a lucrative product that has the potential to markedly improve peoples' lives."

DON'T UNDERESTIMATE THE VALUE OF NETWORKING

Having worked for large, medium, and small companies, Connelly prefers working for a small company, saying, "In this environment, I have the ability to go to conferences, learn about new research areas, and start collaborations and new projects, pursuing my own path. In a large pharma company, a request to initiate a new program would have to go through endless committees. You can get a lot more done with a small company, but you do everything yourself. That's just part of the fun."

In offering advice to her coworkers, Connelly asserts that much of her ability to remain in the networking circuit is the result of her continuing contribution to biotech literature. "I believe it's critical to publish peer-reviewed scientific manuscripts. This is discouraged by some companies, and I feel this is a mistake. As long as ideas and discoveries are protected in patent applications prior to public disclosure, data should be shared with the scientific community for everyone's benefit."

Connelly repeatedly stresses the importance of networking, including at the local level. "I attend monthly meetings of BioBeers in Frederick County, and BioBuzz in Montgomery County, Maryland. It is always fascinating to catch up with old friends and colleagues, and at the same time, you will meet new people and learn what's happening in your local scientific community. Sometimes this may require that you get out of your comfort zone in social situations to develop partnerships as I did when I met the staff of CosmosID [a CRO providing microbial genomic bioinformatics analyses] at an incubator holiday party." Since then, she says those informal conversations moved into a joint program fulfilling her company's microbiome analysis needs.

Over the years and through numerous career changes, Connelly has been able to keep ahead of the game, bearing in mind that "Change is inevitable and you better be ready for it."

Can Private Money Stop The Slump In Global R&D Funding?

SUZANNE ELVIDGE Contributing Writer @suzannewriter

Worldwide, there has been a slowdown, or even a decline, in the growth of public funding for healthcare R&D from public sector agencies and multilateral organizations over the past decade, according to the second Brookings Private Sector Global Health R&D Project from the Center for Technology Innovation at Brookings, titled Private Sector Investment in Global Health R&D: Spending Levels, Barriers, and Opportunities.

The decrease in public funding can impact private sector R&D investment, because public funding often provides support for the basic research essential to the innovation that in turn is an investment target for private money. Cutbacks on spending also can have an impact on public/private partnerships. And the impact is going to be the greatest on the drugs for global R&D – the treatments for diseases most prevalent in developing markets.

"Public funding is falling, but can we rely on private companies to pick up the slack?" asked lead author of the report Darrell West, VP and director, governance studies and founding director for the Center for Technology Innovation at the Brookings Institution.

PRIVATE FUNDING IN GLOBAL R&D

To answer this question, it's important first to understand how private money is spent in pharma R&D. Pharmaceutical companies and venture capital investors already invest a lot in drug development. In 2016, the global estimated spend on drug development was $156.7 billion, and around 60 percent of that was from the top 20 pharma and biotech companies in the West. Chinese pharmaceutical R&D spending was around $7.2 billion in 2016, and R&D spending from Indian companies totaled around $1.9 billion. However, according to the report, just $5.6 billion of worldwide pharma R&D targets global health, that is, drugs and vaccines for the developing world.

Looking at the leading venture capital companies with $1 billion or more in assets under management (AUM), investing in drugs, vaccines, and therapeutics, the authors estimated $69.7 billion in total AUM. Between May 1, 2016 and May 1, 2017, the companies invested $8.9 billion, with $3.3 billion invested in health R&D overall and $225.8 million invested in global health R&D.

"Private companies are not spending on global health R&D, and this is unlikely to change in the short term," said West. "Behind this lies the poor market incentives for private investment in drugs and vaccines for the developing world, as these countries have less ability to pay. The best option is an increase in both public and private funding of global healthcare R&D."

BARRIERS AND SOLUTIONS TO PRIVATE INVESTMENT

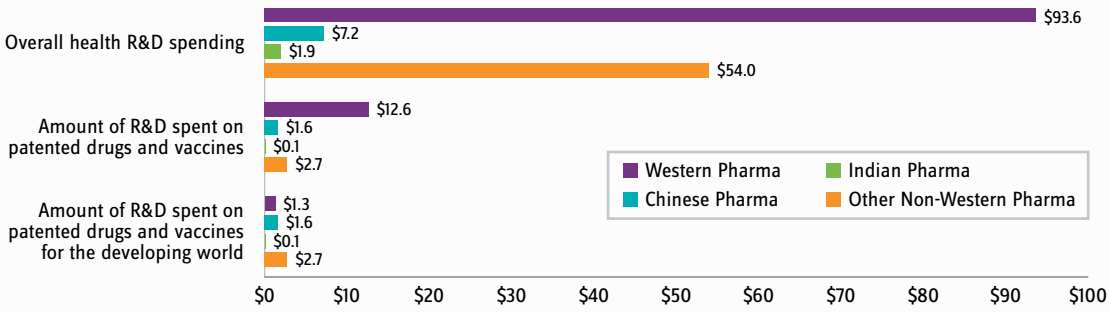
There is a variety of barriers that limit or even block spending on R&D, particularly R&D that focuses on drugs and vaccines for developing countries. These are largely focused on the issues of working in markets where the ability to pay is limited.

"In the developed world, we have access to a lot of drugs. While there are still some challenges with access, these are greater in the developing world," said West.

The challenges include the very high cost of drug development; the macroeconomic difficulties facing private investors; the geopolitical risks in both developed and developing countries; the lack of data on investment returns, infrastructure costs, or the effects of system change on healthcare; and finally, the health governance challenges in the target countries.

There are a number of steps that could help encourage private financing to bridge the gap in the funding. Pri-

HEALTHCARE SPENDING ($BN)



SOURCE: *Private Sector Investment in Global Health R&D: Spending Levels, Barriers, and Opportunities* – Brookings Institution

vate investors may be put off by the idea of investing in pharmaceutical drug development, particularly in developing countries or smaller disease areas, because of the perceived high rate of failure and the limited market size. Better data and more transparency about the development costs, market needs and priorities, as well as the size of the market and the return on investment, could encourage funding commitments.

One of the concerns raised by private investors is a lack of confidence in the health governance, supply chains, and local infrastructure in emerging nations. Thus, innovative solutions in these areas could boost further investment. For example, West says, "While maintaining safety remains important, some countries such as Kenya and Tanzania are improving access to drugs by streamlining the regulatory process and reducing bureaucracy."

Financial inducements also can play a role in boosting private investment, for example, encouraging venture fund investments through redesigned priority review vouchers or providing tax incentives for global health R&D.

THE OPPORTUNITIES FOR INVESTMENT

Increased understanding about the mechanisms behind disease, including better understanding of genomics, proteomics, and biomarkers, means that not only can drugs be better targeted to diseases but also that patients can be stratified according to their likely responses to drugs. This has benefits for a number of different stakeholders. Patients get the best drug for their condition, payers pay for the drugs that are most likely to work, and developers can understand the size of the potential markets. All of these could help stimulate investment, both in developed and developing markets.

There are also investment opportunities surrounding artificial intelligence and computing. For example, new technologies can search databases of existing drugs and suggest drugs that could be repurposed for other diseases.

Investment opportunities also exist outside the traditional markets of Europe and the U.S.

"India and China are investing more and more in drugs and vaccines with lower R&D costs, both for domestic and for regional markets, for example across Asia," said West.

ALTERNATIVE FUNDING MODELS

As funding, whether it's from public or private sources, gets harder to find, some interesting innovative financing models are being developed. "One approach to encourage companies to develop drugs for developing countries is through advance market commitments, where a charity or foundation promises to buy a certain amount of the drug once it reaches the market. Examples of this include the Gates Foundation or the Wellcome Trust," said West.

"Blended finance" is another approach, whereby money from governments, charities, and foundations is used to catalyze private investment. An example is PATH (Program for Appropriate Technology in Health), an international nonprofit based in the United States that drives innovation in vaccines, drugs, diagnostics, devices, and services by mobilizing cross-sector partnerships at many levels, from individuals, through companies and foundations, to governments.

Results-based financing also can play a role. Here, loans or grants are based on meeting certain outcomes or outputs, for example, the impact bond. Here, the investor provides the up-front risk capital, and the outcome funder, such as a government, promises to pay the investor the principal plus interest back if certain outcomes are reached. The investor gains return on investment, and the outcome funder sees an improvement in health outcomes. According to West's report, there are over 80 so-called "impact bonds" across seven sectors, including health, mostly in developed countries.

Finding funding for biopharma R&D, both from the public and private sectors, has become more challenging, particularly for drugs designed for developing countries. Tackling the barriers to private investment and creating alternative funding models could help create innovation for both developed and developing countries.

Navigating The Turbulent Waters From Discovery To Clinical

ED MISETA Chief Editor, Clinical Leader Online

Keystone Nano recently advanced from the discovery phase to a clinical-stage firm, developing nanoparticles that target solid tumors by going after cancer cells and leaving the normal cells intact. But as company CEO Jeff Davidson found, making that transition presents challenges that are difficult to anticipate and can cause disruptions to a development timeline.

"Being a spin-out from academia [i.e., Penn State], we were familiar with early-stage research, and we had access to university resources that permitted us to perform work in discovery, original product development, and analytical testing," explains Davidson. "What was much less available was the knowledge or experience of taking something from the research phase through to preclinical studies and into an IND (investigational new drug). We learned a lot, but that learning curve forced the process to take longer than anticipated."

cGMP MATERIAL CREATES DELAYS

In preclinical testing, Keystone Nano created 13 detailed cGLP studies for its material. With only seven employees, Keystone had to outsource the ingredients and the finished drug product to an external manufacturer. When it came time to move into human testing, the company was confident it had cGMP-quality material and could proceed to the IND stage. Unfortunately the materials turned out to not be cGMP at all.

"We were forced to get exceptionally pure materials manufactured by a different company at a cGMP level. This step forced us to stop and back up. It took us about a year to get a cGMP material that was not only functionally the same but also had enough of the same purity profile that it could be considered the same for IND purposes. We didn't anticipate that."

Davidson notes that if the company had performed scale-up and process development first, it could have gone into the clinic with the material needed. Then, it would not have had to struggle to hit a very high standard of matching. "To be clear, the issue was not over whether the material would cause side-effects in humans. The issue was whether the last two-tenths of impurity could be taken down to one-tenth of impurity," he explains. Ultimately they were able to achieve this ingredient goal and initiate human testing with high-quality materials.

WHEN COST IS A CONCERN

As with any small bio company, cost is an ongoing concern for Keystone Nano. Davidson explains that grants have funded much of the company's work, but those monies are limited. Grants also tend to be time-sensitive, forcing the company's discovery process to adhere to a grant's strict timelines. "If we had more cost flexibility, we would have preferred to produce additional material at the outset of this process. Unfortunately, that wasn't an option."

Finding the right manufacturer also proved challenging. The material produced was highly specialized, and as a result, there were not many companies capable of doing the work. Although Davidson located a supplier relatively early in the development process, it took a while for the two companies to learn to work together. "It's important to identify which company — sponsor or CMO — is responsible for basic actions and activities," he explains. "When some of those activities are left unassigned, individuals on both sides will have differing expectations as to who is responsible for them."

> *"A partnering deal with a bigger pharma company would certainly help us through [the Phase 3] process."*
>
> **JEFF DAVIDSON**
> CEO, Keystone Nano

CONSULTANTS HELP FILL THE GAPS

Another challenge Keystone Nano faced was putting together the needed documentation for the company's first IND application. "In some cases, we knew we needed an expert to guide us through the process," says Davidson. His experience years ago as a founding member of PA Life Sciences (formerly PABio) not only helped him find the talent he needed for his employees but also the consultants the company ultimately used to make sure all the forms were filed correctly according to regulatory guidelines. In fact, he believes that the decision to hire a consulting firm dramatically cut the company's learning curve. "We would not have even known what questions to ask them," adds Davidson.

Being near Penn State also enabled the company to hire M.S. and Ph.D. students quite easily. The students can be put to work on projects right away, without much additional training. Davidson describes them as young researchers with scientific talent who are smart, hard-working, and possessing recently developed knowledge of the field they're working in. Being just a mile off campus also makes the company easy for student interns to access.

RAISING NEEDED CAPITAL

As with any small company's CEO, raising funds to perform research is a key concern for Davidson and one of his primary responsibilities. The company's current Phase 2 trial is partly funded ($2 million) by the National Cancer Institute's Small Business Innovation Research (SBIR) program.

Funding help also came via Pennsylvania's Ben Franklin Technology Partners (BFTP), an economic development program that provides early-stage, technology-based firms with funding, business and technical expertise, and access to resources. BFTP was an early sponsor of Keystone Nano, and Davidson notes that the program was instrumental at helping the company get established and headed in the right direction.

"Universities are very focused on raising money for endowments and special projects," says Davidson. "But, as you might imagine, they can be reluctant to turn that donor information over to startup companies for funding purposes. As a result, we had to build our own resources to secure private equity funds."

What Davidson and Keystone have worked hard to do is raise money from a wide range of sources, including federal and state grants, pharmaceutical and chemical companies, and private investors. This diversity of funding has allowed the company to start a clinical trial on a very modest amount of investor funding, matched threefold by public or nondilutive corporate dollars.

Davidson notes NCI has helped with expertise as well as funding. Keystone Nano knew a lot about its drug product but did not know as much about the clinical trial process. For help with that knowledge, the company recruited, as a co-primary investigator (PI) on the grant, Dr. Edward Sausville, a Phase 1 director from one of NCI's centers at the University of Maryland.

By working closely with Sausville and PIs at the other centers, Davidson has been able to do a better job of anticipating clinical issues, as well as planning and preparing for them. Keystone Nano now has three clinical centers open, the lead institution at the University of Maryland, as well as the University of Virginia and the Medical University of South Carolina. The company is currently looking to expand into two new clinical centers and has strong interest from other clinical centers around the country. Davidson is now interested in completing a partnering agreement with a pharma partner as well.

"We know that Phase 3 trials are very expensive," he adds. "A partnering deal with a bigger pharma company would certainly help us through that process, as they generally come with enough funding to get through a Phase 3 trial. We would love to sign a deal by the end of the Phase 2 trial. Ideally, that would be in the next 18 to 24 months. If that doesn't pan out, we will raise the money through equity funding. We are committed to getting through Phase 3 using one of those two routes." L

The Art Of **Leadership**

CAMILLE MOJICA REY Contributing Writer @CamilleReyATX

Polaris Partners' Amy Schulman is a lawyer by training. She also happens to be an artist. Her medium is the fledgling biopharma startup. From the raw material of amazing science and passionate researchers, she creates successful companies. It's been seven years since Schulman arrived in Boston, leaving behind a job at Pfizer, Inc., where she served as executive vice president, general counsel and was responsible for leading the company's $4 billion consumer healthcare business. Schulman joined investment firm Polaris Partners in 2015. Her first stint as CEO of a Polaris-backed company resulted in the sale of that company, Arsia Therapeutics, to Eagle Pharmaceuticals for $76 million a year after she took the helm.

Schulman says Boston is a vibrant and welcoming environment for biopharma. "It's fast-paced and inclusive. If you've got an idea on how to move a company or technology forward, there is a seat for you at the table."

Today, Schulman serves as CEO of Polaris-backed companies Lyndra and Olivo, is executive chair of SQZ Biotech and Suono Bio, and is on the boards of directors of a list of other companies, as well as the Whitehead Institute. She also teaches legal and corporate accountability as a senior lecturer at the Harvard School of Business. At *Life Science Leader*, we were interested to learn about leadership from someone who has made an art of it.

LIFE SCIENCE LEADER: The failure rate of startup biopharma companies continues to be high. In your job with Polaris Partners, how do you steer a company toward success?

SCHULMAN: I have an understanding of the path — how to get from here to there, from extraordinary science to thriving company. For me, the stumbling block should not be the business model — that's where I can help. The ideal is to be as capable and fearless in business development as the team developing the science. But, it is challenging to fit a game-changing idea into an existing business model. It's our job to define a different, creative business approach. Sometimes the science is a niche play. For others, there are much bigger applications. Understanding the balance and specific potential, while not constraining the platform, is the key.

LSL: You are currently the CEO of two companies and are involved in leading a long list of others. Large or small, how would you describe your role at each company?

SCHULMAN: First of all, I take on companies that are at various stages. So, thankfully, they do not all require the same amount of input. My job, in general, is to translate, refine, and edit the ideas. I am not afraid to dive into the science. I understand what's happening even though the language is not my native tongue. At this point in my career, I relish bringing forth the great ideas of other people. And, in biopharma, that means building a high-performing team that is not unduly anxious and reactive when faced with the inevitable obstacles in drug development.

LSL: What does a startup gain by having an investor/CEO?

SCHULMAN: Ideally, what you gain is the freedom to focus on the science. It's important to not be distracted by early-stage fund-raising and team-building. It's also helpful to have a mentor whose only interest is in seeing the company thrive. But, it really depends on the

"You want people who are always going to be zealous about noticing what doesn't work."

AMY SCHULMAN
Polaris Partners

state of the science and the founding team. One of the requirements that Polaris has is that one of the founding scientists has to stay in an active role.

LSL: What are the challenges you face coming in as an investor and an outsider to a small company?

SCHULMAN: The older I get, the more sure I am that leadership is about other people and never about yourself. That's incredibly powerful. Biotech is a remarkably welcoming intellectual environment. It's not a zero-sum game, as in other business sectors. People are in it because they truly want to improve lives. When I first came to Boston, people were skeptical, and understandably so. They wondered what a Big Pharma executive and a nonscientist had to bring to the table. Despite those questions, the level of acceptance has been remarkable.

LSL: How do you motivate the employees of these companies?

SCHULMAN: The people I encounter in biopharma are highly motivated individuals who are driven to help the world. My job is to empower them and make sure that obstacles don't get in the way. I make sure the culture is consistent with rewarding and sustaining that drive. A company has to give people a chance to grow and learn. People want to give as much as they get. Money is part of that, but caring for the whole person is necessary, too.

LSL: What's the most daunting challenge you see for biopharma startups trying to bring a drug to market?

SCHULMAN: It's such a long haul. You can't be spasmodically reactive to what else is going on in the industry. That is exhausting, distracting, and not sustainable. Part of my job is to say to the team: "I got this." You worry about the things that matter — like getting the science right — and I will build a foundation that will allow us to move forward, thrive, and make good decisions.

LSL: What advice would you give to someone interested in plunging into the world of startups, either as an investor or as an innovator?

SCHULMAN: Be discriminating. It's so easy to fall in love with an idea. Bringing a product to market is tough. It's a road that requires a lot of fortitude. Never, ever compromise on integrity. Follow your instincts. Work with people you like and trust. Don't fail to invest in culture early on. Scientists are used to using intellect in figuring things out. Building a successful team is not intuitive to everyone who comes out of a Ph.D. program, and it cannot be an afterthought in building a great company. Apply the same rigor to building the company that you apply to science.

Scientists are born optimists. They use logic to figure things out and make things work. Optimism bias is critical to get through the early stages of drug development. But, at some point, you need to figure out how to temper that optimism with reality. That means having a team that knows how and when to push back. This is critical if the company is going to endure and grow. Culture really matters. Unfortunately, it's often overlooked. If the culture is right from the beginning, you will find you get better, faster solutions to the problems that arise. Multiple perspectives need to be empowered to engage and integrate the science with the business. You want people who are always going to be zealous about noticing what doesn't work. And that can't happen if people are working in silos or leaving half of their brains at the door because they are not encouraged to contribute. Everyone must feel they are part of a team; that they are learning, growing, and that their input is valued.

LSL: What have you learned about leadership since taking on executive roles at fledgling biopharma companies?

SCHULMAN: I have learned that leadership is an art form — not a set of discrete principles that follow the same order for every company. You need to trust your intuition and use creativity. There is an intangible element to success. It's different for every company, and, for each one, it will be revealed to you if you allow yourself to lean into what the company needs. The best leaders balance control, vision for where the company's going, conviction, and a tolerance for ambiguity. Each company and leadership team is not comfortable with the same proportion of those things. But every company needs a leader who can deploy those skills variably and responsively. That's something that we should aspire to as leaders.

The Missed Opportunity **Of Medical Affairs**

GAIL DUTTON Contributing Editor @GailLdutton

If you're not using medical affairs strategically, you're missing an important opportunity. As the voice of science, these specialists are more than just a support function. Today, they are shaping conversations with physicians and even with payers. They are probing deeper, spotting shifts in stakeholders' interests and competitors' communications strategies that can be leveraged to support activities throughout their own companies.

The change from support function to strategic asset was catalyzed by the growing complexity of therapeutics during the past 15 years. Biologics became mainstream, and molecular medicine expanded, introducing complex mechanisms of action and companion diagnostics to stratify patient populations. Fully communicating the value of these new options requires strong scientific expertise.

Changes in healthcare also have shifted conversations. Payer acceptance depends upon product differentiation as well as efficacy, risks, benefits, and cost. Medical science liaisons (MSLs) must be well-versed in these aspects as well as in a therapeutic's scientific merits.

"Pharmaceutical companies started to understand that physicians need more information than data sheets contain," says Hartmann Wellhoefer, M.D., head of medical affairs for rare disease and internal medicine at Shire. "Physicians need more context for disease education to better understand the safety, efficacy, and mechanisms of action, especially for complex biologics."

Those needs extend to payers, too, notes Zhen Su, M.D., MBA, chief medical officer at EMD Serono. "Outcome liaisons — a subset of MSLs — are working with payers to convey the value as well as the efficacy of interventions." That includes generating models based on real-world data, local adaptations, payers' treatment flows, and budgetary impacts.

As the result of those changes, Wellhoefer says, "Medical affairs has become an independent function within R&D. We're more professional in how we do things."

That often includes functioning as a facilitator for physicians and their patients. Rare diseases (which compose three-quarters of Shire's clinical pipeline) usually are diagnosed extremely late, so understanding the disease is a key goal. Shire's MSLs, therefore, focus on understanding the fundamentals of a disease. That includes the patient journey, unmet medical needs, and how the disease presents outside clinical trials. "They use that information to help the company design clinical trials, discuss our products, and select priorities," Wellhoefer says. "Our goal is to help physicians and patients use our compounds appropriately."

"Because we're living more digitally, we can measure things we couldn't measure before."

HOLLY SCHACHNER, M.D.
VP, Head of medical affairs in North America, Sanofi

USE METRICS TO CHANGE THE KOL CONVERSATION

During the past decade, CRM tools have tracked interactions with KOLs, healthcare providers, payers, and other stakeholders as a measure of success. To gauge a publication's success, medical affairs tracked the numbers of journals in which its data appeared, the journals' impact factors, and how often those papers are referenced by others.

Now, a new generation of analytics platforms is enabling deeper analysis and is helping MSLs have focused conversations with thought leaders.

"Because we're living more digitally, we can measure things we couldn't measure before," says Holly Schachner, M.D., VP, head of medical affairs in North America for Sanofi. Share of scientific voice is one example. "Share of scientific voice is a qualitative measurement of the number of mentions generated by a blog or tweet, as well as abstracts and papers." By including it, she knows whether her team's scientific communications efforts are generating a buzz that is being picked up by others.

These new analytics platforms comb the internet for information that's valuable specifically to medical affairs. For instance, they can search papers and presentations by author, topic, journal, or meeting, or search KOLs' networks for related research or potential co-authors. MSLs can analyze that data to see trends and changes in scientific contributors' publication or presentation frequency, research interests, and sponsorships.

Equipped with this knowledge, "When MSLs go to meetings, they have a deeper understanding of their KOLs' opinions and interests, so conversations can be more scientifically stimulating," elaborates EMD Serono's Su. "Our KOLs tell me our people are more prepared."

This deep preparation also helps reveal any scientific misconceptions that MSLs can correct. "That actually happens quite a lot," Su says. "There's too much information for people to be aware of it all. Helping with key data points makes MSLs very trustworthy."

Medical affairs analytics platforms may be most helpful in identifying potential co-authors and sub-investigators who are relatively new to the field, suggests Schachner. "Deciding with whom to work is a complex determination that can't be made based on data alone."

Reliance on digital analytics platforms is only one approach, of course. "If my team needs analytics platforms to gauge the pulse of the scientific community, they've missed the boat," Wellhoefer states.

To generate the insights his team needs, Wellhoefer hosts approximately 10, one-to-two-day workshops per year for about a dozen medical affairs professionals. "We bring in our cross-functional experts, review what was published in the past year, and match that with our evidence planning, KOL insights, and market research to identify trends and gaps."

SHARE INSIGHTS THROUGHOUT YOUR COMPANY

Throughout the year, Shire's MSLs enter details from each KOL contact into a central database. "This gives us one view of the customer from which to gain insights," Wellhoefer says.

Sanofi's MSLs do that, too. Afterward, the data is filtered and evaluated by a cross-functional team that may include commercial representatives. "We see what actions need to be taken to close data or educational gaps and determine where we need to focus," Schachner explains.

"Sometimes clinicians stall and can't achieve their clinical goals," she continues. MSLs need to understand where and why they stall and then provide whatever is needed to help them past their roadblocks. Sanofi's solutions have included providing titration tools as well as education.

Understanding the value proposition and closing gaps in evidence is vital for the company, too, because those details affect how products are prioritized, presented, and launched. Combining medical affairs insights with those of other departments — without breaching firewalls – helps do that. One advantage of sharing perceptions, Wellhoefer says, is that "The commercial side has insights into communication tools and methods and ways to analyze what people understand about a product that can help scientific communicators."

Su advises distilling the disparate information, identifying recurrent themes, and digging deeper to learn why those themes emerged. Evaluating this diverse info lends insights into, for example, how competitors are handling similar products pre-launch. This opens discussions into the pros and cons of differing communications and therapeutic approaches that may affect payers' perspectives. It may even hint at a competitor's thoughts about a product and the market it will enter.

"Such early indicators are taken quite seriously," Su emphasizes. "If you wait to act until data is published, there's almost a year's lag-time. Online publications lag by about six months."

HOW MA AFFECTS CLINICAL TRIALS

This new, data-driven approach to medical affairs sharpens decision making and can shape KOL communications and even trial designs. For example, Su says, "We look at who KOLs are talking with in terms of other companies and thought leaders. This gives us insights into our competitors' intelligence," by understanding what these scientists are saying in the scientific literature. Connecting those dots helps reduce any communications ambiguity and evidence gaps.

"Medical affairs has become an independent function within R&D."

HARTMANN WELLHOEFER, M.D.
Head of medical affairs for rare disease & internal medicine
Shire

In terms of clinical trials, "Some 20 to 30 lung cancer trials are ongoing at any given time," Su says, so competition for sites and investigators is stiff. "If competitors are planning to run studies similar to ours, we know and can reach out to study sites early to potentially secure their enrollment." Waiting risks losing access to those sites for one to two years, as well as the potential for failure if the replacement sites have operational issues or lack experience conducting complex trials.

At Shire, when disproportionate numbers of patients dropped out of its short bowel syndrome (SBS) trials, medical affairs wanted to know why. "No other product was out there, so no one understood what the compound would do outside clinical trials," Wellhoefer recalls.

Working with centers of excellence, his medical affairs team sought to understand the natural history of SBS. Deeper analysis of patients revealed patterns, which MSLs shared with treatment center experts. "We had very robust discussions and ultimately realized there were two distinct populations that responded very differently to our product," he recalls. One group responded within weeks, while the other took up to six months to respond. The difference, they learned, depended on whether the syndrome developed gradually or occurred because of trauma. With this information, MSLs could advise physicians who suddenly could predict response times for their patients.

Working with thought leaders to generate this sort of data and providing it to physicians cements the perception of medical affairs professionals as the voice of science. Sharing the insights and trends during those interactions cements their value to their companies, by providing a current, more detailed analysis of the scientific landscape than ever before.

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Deal Building From Testing The Water To Hitting The Market

SUZANNE ELVIDGE Contributing Writer @suzannewriter

In 2017, UK-based gene and cell therapy company Oxford BioMedica won a key contract from Novartis to provide the commercial and clinical supply of lentiviral vectors used to produce Big Pharma's CAR-T cell therapy Kymriah (tisagenlecleucel). The deal could be worth upwards of $100 million over its three-year span.

2011-2013: BEGINNING THE CONVERSATION AND TESTING THE WATER

According to John Dawson, Oxford BioMedica's CEO, the relationship between Oxford BioMedica and Novartis dates to initial conversations in 2011, which developed further through 2012.

"We started by testing the process and optimizing the vector," said Dawson. "And then in 2013, we signed an initial agreement with Novartis to manufacture clinical-grade material using our LentiVector gene delivery technology and to provide process-development services. We manufactured a number of batches of the lentiviral vector encoding the tisagenlecleucel technology, but at that point neither we nor Novartis had made a formal long-term commitment."

The initial deal was worth up to $5.2 million from Novartis over 12 months and allowed Oxford BioMedica to make strategic investments in its specialist manufacturing capabilities, which Dawson described as a pivotal step toward building a financially self-sustaining business, as well as an example of how the company could commercialize its expertise.

OCTOBER 2014: BUILDING THE DEAL

In 2013 and 2014, Novartis' tisagenlecleucel moved through Phase 2 trials, and in October 2014, the two companies signed a further cash and equities deal, building on the previous agreement. This included a $14 million up-front payment from Novartis, including a $4.3 million equity subscription for a non-exclusive worldwide development and commercialization license in oncology for Oxford BioMedica's LentiVector platform. The manufacturing deal would be worth up to $90 million in total over three years, including the up-front license payment, equity investment, manufacturing and process development services

"While we're not yet EBITDA positive, this deal with Novartis will strengthen our balance sheet immediately and support our continued growth over the next three years."

JOHN DAWSON
CEO, Oxford BioMedica

OXFORD BIOMEDICA PARTNERSHIPS

PARTNER	PRODUCT	INDICATION	STAGE OF DEVELOPMENT
Sanofi	SAR422459	Ophthalmology: Stargadt disease	Phase 2
	SAR421869	Ophthalmology: Usher syndrome type 1B	Phase 1/2
Novartis	Tisagenlecleucel	Oncology: r/r ALL	Approved (US)
	Tisagenlecleucel	Oncology: r/r DLBCL	Phase 2
	Undisclosed CAR T	Oncology	Phase 1/2
Immune Design	CMB305	Oncology: Advanced, relapsed, or metastatic sarcoma	Phase 2
	LV305	Oncology: Various cancers	Phase 2
Orchard Therapeutics	ADA-SCID	Metabolic disorder: ADA severe combined immunodeficiency	Phase 2
	MPSIIIA	Sanfilippo syndrome	Preclinical
GlaxoSmithKline	Undisclosed	Undisclosed	Phase 1/2
	Undisclosed	Undisclosed	Phase 1/2

CHART 1

and various performance incentives. Under the terms of the deal, Oxford BioMedica is the sole manufacturer of the lentiviral vector used to transfect the T cells to produce tisagenlecleucel.

The October 2014 deal also included an exclusive license for the worldwide development and commercialization of all CAR-T cell products arising from the process development collaboration. Oxford BioMedica will receive undisclosed royalties on potential future sales of all Novartis CAR-T products, including tisagenlecleucel.

"This deal was part of Novartis' preparation to move its cell therapy onto the market, and its commitment endorsed our approach and capabilities," said Dawson.

2016: DESIGNING AND BUILDING

Oxford BioMedica began 2014 with only one GMP suite. Because of the investment made possible by the deal with Novartis, and through the deals with other companies for its LentiVector technology platform, the company was able to create a state-of-the-art GMP manufacturing facility to manufacture the batches for clinical trials. In 2016, it also had a warehouse facility up and running.

In 2016, Oxford BioMedica completed a design-and-build program, creating new bioprocessing and laboratory space. This included three cleanrooms, with cell factories and single-use 200 liter bioreactors in dedicated production suites.

"By optimizing our processes, we have been able to cut the cost tenfold; however, we plan to reduce costs further by continuing to innovate. When we get to scale-up stage, we should be able to keep the same process, perhaps with minor changes. We are confident we can hit the ground running as we are already making commercial products," said Dawson.

With CAR-T therapeutics currently priced in hundreds of thousands of dollars per patient, being able to cut manufacturing costs could be critical for ensuring that more patients can gain access to treatment.

2017: GETTING TO THE MARKET

The deals with Novartis have been structured to generate income from sales of the CAR-T products. Oxford BioMedica has, therefore, been watching the progress of the regulatory process very closely, as Kymriah could be a key driver for revenue over the next few years.

In March 2017, the FDA accepted the biologics license filing for Kymriah and granted it a priority review designation, which would shorten its anticipated review time. This and other planned activity for 2017 and 2018 needed to be backed up with a manufacturing agreement. So, in July 2017, Oxford BioMedica announced signing a major supply agreement with Novartis for the commercial and clinical supply of lentiviral vectors used to generate tisagenlecleucel and other undisclosed CAR-T products.

As in earlier deals, the overall amount ($100 million over three years) includes an up-front payment ($10 million), various performance incentives, and bioprocessing and development services. The supply agreement is extendable to five years subject to the agreement of both parties.

"Putting together this deal was a detailed process that involved both FDA and MHRA [Medicines and Healthcare products Regulatory Agency] inspections. We anticipated being at this point, which was why we spent £26 million [approximately $35 million] in developing the GMP suite in 2016. So we had to be successful! Now that we have the facility, we can plan for future deals," said Dawson. "While we're not yet EBITDA positive, this deal with Novartis will strengthen our balance sheet immediately and support our continued growth over the next three years. It is also a great validation of our approach and technology."

In mid-July 2017, Kymriah gained a unanimous recommendation from the FDA's Oncologic Drug Advisory Committee in favor of approval. Around six weeks later, Novartis' Kymriah became the first CAR-T therapy to be approved worldwide. This approval, for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL), was five weeks before the proposed Prescription Drug User Fee Act (PDUFA) date of early October. Kymriah has been followed to U.S. approval by Kite's Yescarta (axicabtagene ciloleucel), a CAR-T cell therapy for adult patients with certain types of large B-cell lymphoma (BCL) who have not responded to other treatment or who have relapsed.

As a result of the activity over Kymriah, Oxford BioMedica has seen its share price more than double over the course of 2017.

2018: THE FUTURE FOR OXFORD BIOMEDICA – IN-HOUSE AND PARTNERING

Oxford BioMedica has 20 years of experience in gene and cell therapy and eight years of clinical experience with its lentiviral platform. This expertise has led to seven regulatory approvals for clinical studies in the United States and Europe. The company is growing fast, as Dawson explains: "In January 2014, we had just 80 people. We now have around 300 in manufacturing and research. We need to keep working to stay ahead of the game; we can't afford to stand still in this field."

In 2016, Oxford BioMedica completed a design-and-build program, creating a new bioprocessing and laboratory space.

While working with Novartis has been hugely important for Oxford BioMedica, Dawson is keen not to rely too much on a single partner or product.

"We have bioprocessing and process development partnerships (Chart 1) with Immune Design and Orchard Therapeutics. We also have licensed products and technology rights to Sanofi, technology rights to GlaxoSmithKline, and an R&D collaboration with Green Cross to identify and develop gene modified natural killer cell-based therapeutics for diseases like cancer," said Dawson.

There are four products in Oxford BioMedica's in-house pipeline (Chart 2), and the company's business plan is to develop products to preclinical and then seek partners.

"We plan to progress our wholly-owned products via spin-outs and out-licensing opportunities, while continuing to invest in our LentiVector platform. We are hoping to set up significant deals over 2017 and 2018 to ensure long-term funding through royalties," said Dawson. "We could look to take projects further into development in the future if we have the funding."

Dawson is confident of the company's future and says: "We want to become the world leader in lentiviral vectors, both in vivo for gene therapy and ex vivo for cell therapy."

OXFORD BIOMEDICA'S IN-HOUSE PIPELINE

PRODUCT	INDICATION	STAGE OF DEVELOPMENT
OXB-102	CNS: Parkinson's disease	Phase 1/2 trial preparation
OXB-202	Ophthalmology: Corneal graft rejection	Phase 1/2 trial preparation
OXB-201	Ophthalmology: Wet age-related macular degeneration	Phase 1 complete
OXB-302	Oncology: Various cancers	Preclinical complete

CHART 2

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Senior Director, QA, Product R&D
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Is Your Lab Prepared For A Cybersecurity Attack?

GARY GRECSEK & RAN HAREL

The pharmaceutical industry has become a prime target for cybercriminals; especially pharmaceutical R&D labs. These ever-changing environments are filled with tools and devices that vary in innovation, age, origin, and brand, and many are operated in distributed facilities across the globe. In addition, the data in these labs ranges from proprietary information related to breakthroughs to individual patient data.

New and complex threats are popping up every day from cybercriminals and from inside the organization, ranging from disgruntled employees stealing data to personnel accidentally clicking a malicious email link. While the costs and reputational implications associated with breaches are enough to pay heed to cybersecurity, these compromises can pose a serious threat to patient safety: Hackers can mislabel drugs and tamper with formulas.

The average cost of data breaches reaches at least $3.63 million (Ponemon Institute). Pharmaceutical organizations must do more than arm their IT departments with technology to detect and thwart cyberattacks; they must have a plan in place to remediate in the event of a breach. From experience, we have found that a few key components need to be in place when a cybersecurity event happens:

- **VISIBILITY INTO ALL NETWORKED DEVICES** – At the first notification of a breach, a fog-of-war situation can arise. From the C-suite to IT, people are scrambling to understand what happened, how to stop the attack, and quickly assess the damage. Having continuous visibility into all networked devices, as well as stand-alone and hybrid solutions, can add context, such as how and where the breach occurred. Having that level of visibility can expedite the incident-response process.
- **BACKUPS OF ALL ASSETS** – Validation and verification of laboratory equipment is required by the FDA to ensure the instrument is producing consistent, accurate results and provides objective evidence to support compliance and reporting. This can include testing, inspection, and analysis and can take anywhere from hours to days per instrument, depending on the complexity of the device or system. When an organization or lab has experienced a cyberattack, all device applications, configurations, and firmware must be revalidated and verified, which can slow down the remediation process. While most organizations have backups of their data, many forget to include their device applications, configurations, and firmware. A complete and accurate backup includes these three compliance components together in a validated state, saving critical time to getting labs back online quickly and efficiently.
- **A BUSINESS-CONTINUITY PLAN** – This plan helps to ensure that assets and personnel are protected and able to function if a disaster or cyberattack occurs. Considerations range from having validated and complete backups of both data and device configurations, to making sure phone numbers are available in hard-copy form so the response team can stay in contact in lieu of electronic resources. Vendors also have to be a part of this plan. Once a plan is in place, test multiple times to identify gaps and ensure everyone understands their roles and responsibilities and are ready to react quickly.

The lab of the future is digital, and as global pharmaceutical companies become more connected, the ability to control potential attacks becomes increasingly difficult. Being prepared, assessing risk, and putting an operating system in place can make organizations more nimble, aware, and ready to react with minimal impact in the unfortunate event that a breach occurs.

GARY GRECSEK is VP and general manager of PerkinElmer Health Sciences, Inc.'s OneSource Global Laboratory Services.

RAN HAREL is VP of products at Halo Digital.

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How To Create & Sustain A Culture Of Accountability

SYLVIA LAFAIR, PH.D.

SYLVIA LAFAIR, PH.D. is the author of *Don't Bring It To Work.*

In my work with senior executives and management teams, one issue that is complex and constantly uncomfortable centers around discussing accountability. For many, just the word itself sets people on edge.

The blame game is immediately activated, and leaders put their energy into figuring out how to help those lazy, annoying, or ineffective employees they label procrastinators, rebels, or avoiders. The underlying idea, sadly, is to see the problem "out there." It's a common way to feel safe and not have to look at personal behavior that may be at the heart of the issue.

Bring the concept closer to home, and you see eyes look down and bodies tense up. The stance quickly becomes one to defend, explain, and justify why others are to blame.

WHY IS THIS BEHAVIOR SO COMMON?

Why is it difficult, even painful, to discuss personal accountability? The closer it gets to the leaders of the company, the more it may be avoided. Many hope that, if you ignore the situation long enough, it will simply go away or perhaps just right itself.

Often, leaders will send an underling to discuss issues about poor project results or lessened sales. They are tasked to find the problem person and make adjustments.

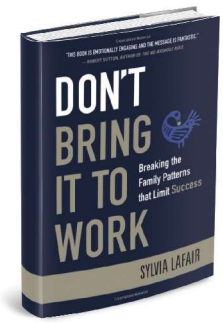
No one wants to be blamed when the initial intentions were good and things didn't work out. Yet, not speaking up and taking responsibility is much more detrimental.

Accountability starts at the top and rolls downhill. What gets modeled by the leaders will show up at every other level of the organization.

Let's face it, being accountable and holding others accountable takes courage. It may seem easier, at least less stressful, to avoid being and holding others accountable. Hoping for the best often gets you the worst.

Here is a 10-step process to help you stay on point and be accountable, no matter what:

1. **START WITH THE END IN MIND:** Be crystal clear about the outcome you expect.
2. **PAINT THE TOTAL PICTURE:** Indicate up front what measurements are being put in place to ensure success.
3. **WHO DOES WHAT:** Be specific about what individuals and teams must complete and by when.
4. **CREATE A DIALOGUE:** Set meetings to communicate and discuss the strategies being used and find ways to make changes as necessary.
5. **PROVIDE RESOURCES:** Have a specific list of needs (not wants) agreed to and set out with time lines for everyone to see.
6. **GIVE AND GET CONTINUOUS FEEDBACK:** Make this fact-based and not blame-based. Stop the finger pointing immediately, or it will destroy morale.
7. **PRACTICE KAIZEN:** Focus workers on continuous small improvements on a daily basis.
8. **ACKNOWLEDGE AND ENCOURAGE:** Stay in the positive zone, especially when there are setbacks, to keep the momentum going.
9. **BE OPEN:** Discuss issues without JUBLA (judgment, blame and attack), and be responsible to *own* your mistakes and miscommunications up front and out loud.
10. **SHARE IN THE SUCCESS:** Take part in the success, don't be overly humble, and make sure others are also appreciated in front of the team.



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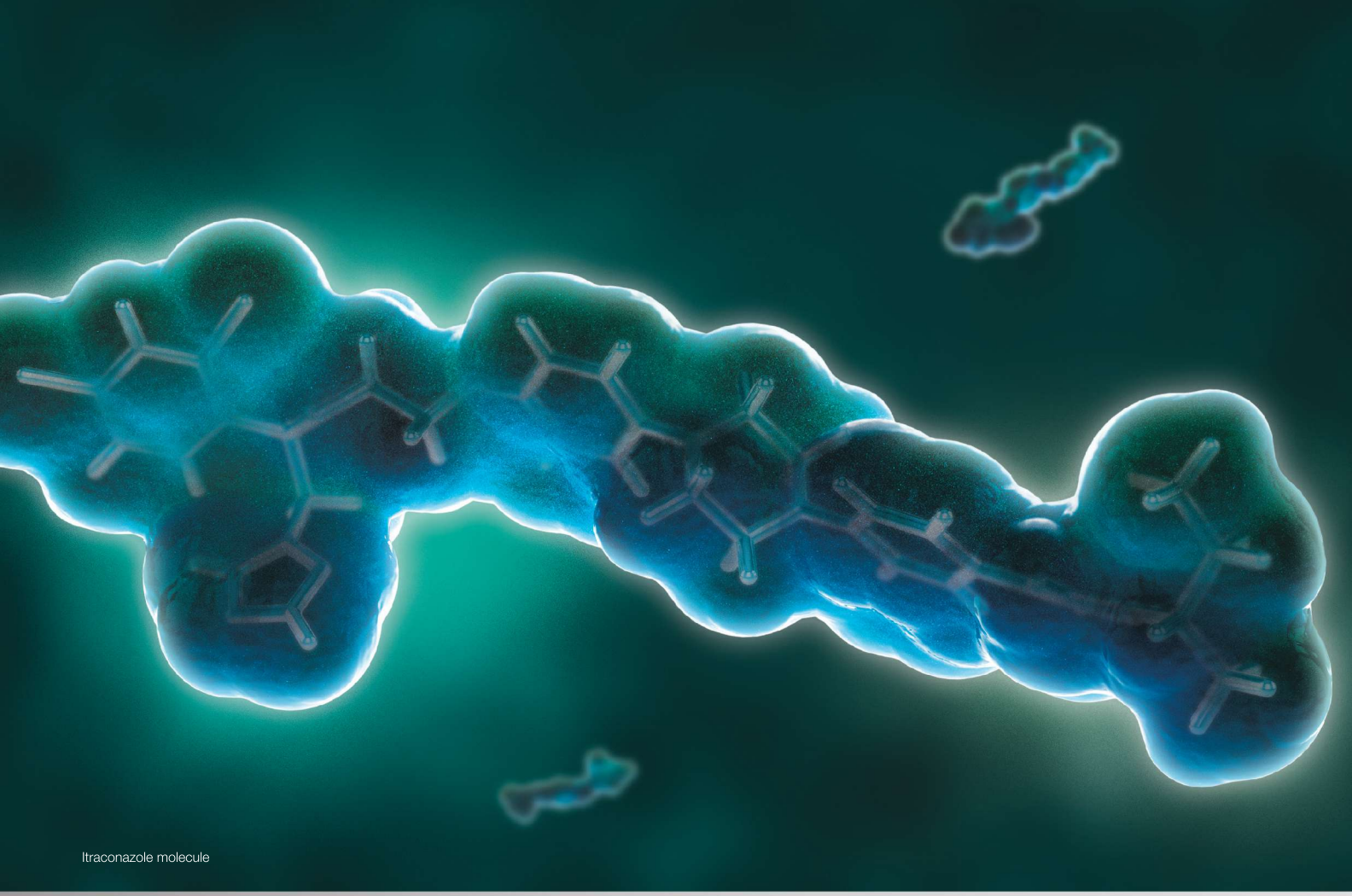

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