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Brexit Shmexit — Let's Keep Calm And Carry On

ROB WRIGHT Chief Editor

The "Keep Calm And Carry On" saying (so popular of late) has been revised in countless varieties and is showing up on everything from coffee mugs to emojis. And while you might think wearing a Keep Calm T-shirt makes you trendy, let's remember the context of where and when the phrase had its origins (i.e., a 1939 British government slogan prior to WWII). It seems especially important during these days of Chicken-Little type reaction to the UK's referendum to "Brexit" the EU. Not surprisingly, on the day Brexit was first announced (Friday, June 24), the markets responded with the Dow Jones industrial average (DJIA) and the NASDAQ composite index losing 609 and 200 points respectively. Considering such a negative market reaction, one might expect the converse when it was first announced that the House of Commons had approved the UK's membership to join the European Economic Community (EEC) on Thursday, October 28, 1971. However, the move was not met with market jubilation, but more of a yawn, with the DJIA closing up from the day previous by only 1.24 points. Maybe we should keep calm and breathe easy on Brexit. After all, the process of the UK exodus will take years, and will first require a parliamentary vote approving the move. And for those worried about the process of disentangling the UK from the EU, from a life science perspective, it should be somewhat easier. Because though the EMA (the drug regulatory agency for EU members) was founded in London in 1995, the UK, like every other EU member, continued to operate its own regulatory agency (i.e., Medicines & Healthcare products Regulatory Agency).

Not long ago, a colleague asked if we should be doing more to cover Brexit. They believed this to be a "massive anti-globalization event" that could have dramatic implications for the life sciences industry. I agree this could be a significant worldwide event, but I also feel there are plenty of folks rushing to analogize Brexit as a "time bomb" that will leave most of European pharma outside of the EU. For example, one article listed which European pharmaceutical companies will be domiciled outside the EU following Brexit. Looking at the list, I found it interesting that Switzerland is where the top two — Novartis and Roche — reside. A country sitting at the geographic center of Europe, Switzerland, is not a member of the EU, and yet, according to a report published by the World Economic Forum (WEF), ranks first of the 10 most competitive European economies. Further, Switzerland has been sitting atop WEF's global competitive index (GCI) for seven years in a row, beating out Singapore (2) and the United States (3). Not being a member of the EU doesn't seem to have hurt the Swiss. As such, perhaps an argument can be made that there is more to be gained by the UK opting to go it alone. For though the majority of the GCI top 10 come from EU member countries (i.e., Germany [4]; the Netherlands [5]; Finland [8]; Sweden [9]; and the UK [10]), I wonder if they may have fared better had they not been burdened with carrying several of their less productive EU counterparts (e.g., Greece). Sure, untangling the UK from the EU — should it actually happen — will present challenges. But instead of expecting the Brexit sky to fall, perhaps we can keep calm, for within adversity there always resides opportunity. L

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Q What simple solutions can biopharma executives implement to positively impact public perception?

A IT WILL TAKE A SUSTAINED EFFORT, NOT "SILVER BULLETS," to turn the public perception tide. Collectively, industry professionals – and leaders in particular – need to be passionate, yet thoughtful advocates for the science that motivates us every day. While it is tough for individual CEOs to justify public actions that go beyond the immediate needs of their own companies, public personalities such as Elon Musk or Steve Jobs illustrate the impact a vocal leader can have on shaping a company or industry's image. Biopharma has generated discoveries that rival Tesla and Apple's global impact, and yet the public doesn't seem to appreciate their significance. To proactively shape how society views biopharma, not only do we need to proudly integrate our work into our public identities, but share these efforts by regular engagement with traditional and social media outlets.

HEATHER ERICKSON
is the former president and CEO of the Life Sciences Foundation, the independent steward of biotech heritage. Previously, she was founding President of MedTech Association, serving New York's bioscience community.

Q What mechanisms can be used to encourage U.S. companies to bring back their overseas "stranded capital"?

A THE U.S. IS AN OUTLIER AMONG THE MAJOR INDUSTRIALIZED NATIONS IN:

- Taxing its corporations on overseas profits (unless overseas cash is declared as "permanently reinvested")
- Having a relatively high corporate tax rate of 35 percent

This has created bloated offshore cash pools among large U.S. corporations. In 2004 a repatriation tax holiday at a 5.25 percent tax rate enabled $360 billion worth of capital to be injected back into the American economy. Until Congress can get unified on long-term tax reform (possibly in 2017), another similar tax holiday would be a good idea to reduce these distortions caused by stranded capital overseas.

FRED HASSAN
is the managing director at Warburg Pincus and former chairman of Bausch & Lomb. He has served as the CEO of several pharmaceutical companies and chaired significant pharmaceutical industry organizations.

Q Knowing what you know now, what would you do differently in founding a biopharma company?

A THE MOST IMPORTANT LESSON I'VE LEARNED CAME FROM MY CURRENT COMPANY: Do *not* develop innovative products for devastating unmet medical needs whose care is dominated by public health officials and advocacy groups. It's an exhausting uphill battle with funders (2 million people die, but can we even recover our investment?), nonprofits (small companies are too financially unstable for grants), advocacy groups (for-profit companies are clearly in it for money, not to cure patients). No good deed goes unpunished in this community. If you want to *enjoy* the experience of building a business that can make a huge difference in the life of patients, go with the flow! Today it's immuno-oncology. If I hurry I can finish what we started 19 years ago, new drugs for tuberculosis, and move on to something both fun and fundable. By then immuno-oncology will be out of favor and there will be a new bandwagon to consider.

CAROL NACY, PH.D.
is CEO of Sequella, Inc., a private company that develops new anti-infective drugs. She was formerly CSO at Anergen and EVP/CSO at EntreMed.

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WAYNE KOBERSTEIN Executive Editor
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SNAPSHOT

Enteris is developing its own pipeline of drugs converted from injectable to oral formulation with its proprietary technology, Peptelligence. Its lead product candidates are Ovarest (oral leuprolide tablet), in preparation for a Phase 2 trial in endometriosis later this year; and Tobrate (oral tobramycin tablet), on track to enter Phase 1 in uncomplicated urinary tract infections (uUTIs), also later this year.

WHAT'S AT STAKE

Businesses that were once happy to play a supporting role in development by supplying goods and services to developers are starting to think bigger. I chose one of them, Enteris BioPharma, in good part to see why and how a contractor would make the transition from pure "partner-supplier" to developer of its own pipeline. "When you're working for other companies, there are two disadvantages — one, you don't have full control of your destiny; two, the work tends to come in peaks and valleys," says Enteris chairman and CEO Joel Tune. "So we started our own drug development with the idea that we would fill the peaks and valleys, and we could ensure our investors we were in a position where we had control of our own destiny with a valuable asset."

Enteris also offers another take on specialty-drug development — not every company entering this space looks at it as an easy gold mine. Combining a generic product with its proprietary formulation technology, Peptelligence, Enteris may succeed in creating value without exploiting the expectation of huge profits.

Enteris came into being only three years ago, having bought the technology that incorporates a peptide or hard-to-deliver small molecule into a tablet. As a CMO, it works for Big Pharma companies and with smaller companies such as Cara Therapeutics, for which it has formulated, and produces, a new kappa-agonist pain med in development. Although the first indication for the company's own lead compound, oral leuprolide, is for endometriosis, other indications will follow, with fibroid tumors at the top of the list, according to Tune. Tobramycin is an old antibiotic that has always been given intravenously or pulmonary; no one else has succeeded in making it in an oral form. In the first indication planned for the oral form, uUTIs, tobramycin has essentially never been used, so it has not generated the resistance plaguing antibiotics now in use for the condition.

"Endometriosis is about a $600 million opportunity, and uUTI is about a $400 million opportunity," says Tune. By today's standards, those figures may seem quite moderate. Although a commercial partner would obviously have a say in the matter, pricing will stay modest if Enteris sticks to its current plan. "We have assumed no price increase over what's currently in the marketplace, even though we believe we have a superior product," Tune says. "We did in-depth interviews with physicians, patients, and payers, and we got a positive response from all of them. Leuprolide is arguably the most effective agent for treating endometriosis, but people are reluctant to use it because the only forms available in the U.S. marketplace are 30-day or 90-day injections."

Enteris has an interesting constraint on its clinical development — like its smaller partners, to some extent, it is also a virtual company. Most of its employees are chemists in formulation and manufacturing, so it seeks outside expert advice and uses a CRO for clinical trials. But it can schedule trials only when its CRO has a slot available. For trial design, it has tapped the talent and experience of people who have immigrated from Big Pharma to small biopharma because of large-scale consolidation and associated layoffs. By thus combining the old and the new, in all the ways described here, the company may epitomize an innovative model for entrepreneurial drug developers.

JOEL TUNE
Chairman & CEO

Vital Statistics

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Headquarters
Boonton, NJ

Finances

Total Raised
$15M

VC Rounds
$15M

Lead Investor
Victory Park Capital

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If Government Fails, More Government!

JOHN McMANUS The McManus Group

When government-run healthcare fails, what is the left's solution? More government!

In June, the Obama administration's Office of the Actuary issued the Medicare Trustees report, which determined "The Hospital Trust Fund is not adequately financed over the next 10 years." The trust fund will be depleted by 2028, two years earlier than last year's estimate.

Less than a week later, President Obama called for a "public option" — based on Medicare's raft of fee schedules and regulations — to be provided in the struggling healthcare exchanges to compete against private insurers.

Now Democratic presidential candidate Hillary Clinton is calling for an expansion of Medicare to individuals as young as age 50. (No coincidence this is the AARP eligibility age). The Medicare expansion could add as many as 13 million people to the rolls, according to an Avalere analysis. The program is supposed to allow individuals lacking employer coverage to buy in to Medicare, but their risk profile means that Medicare will shoulder much of their costs. And government would have more people, younger people to barter with.

Medicare is going broke. No problem; add more beneficiaries to the rolls!

The left's appetite for ever-more government intervention into healthcare appears to be whetted, not satiated, by previous intrusions.

President Obama published a legacy-seeking article in the *Journal of the American Medical Association* (JAMA) touting the success of the Affordable Care Act, notably the decline of the uninsured from 16 percent to 9.1 percent. Certainly, a 40 percent drop in the uninsured is noteworthy. But almost the entirety of the coverage expansion was due to Medicaid expansion in 31 states, opting for federal funds, not from healthcare exchanges.

Joel White, president of the Council for Affordable Health Coverage, testified at the July 12, 2016 Ways and Means Committee hearing: "Despite the broad array of available health plans and a tax for being uninsured, many of those who had been expected to sign up for coverage — even those eligible for subsidies — have not done so. In fact, enrollment is only about half of what the CBO (Congressional Budget Office) projected when the law was first passed." Right-o!

It turns out that the Obama administration went to extraordinary lengths to prop up the health plans in its exchanges, including illegally funneling cash to the plans in direct contravention of statutory law. An exhaustive joint investigation by the House Ways and Means and Energy and Commerce Committees released in July reveals that the Obama administration has been illegally dispensing funds to insurance plans through the "cost-sharing reduction" program to reduce deductibles and copays for certain low-income enrollees that were never appropriated by Congress. Under the ACA's (Affordable Care Act's) clear statutory language, those funds cannot be provided unless Congress appropriates the funds each year. In 2013, the then-Democratically controlled Senate refused to provide those funds, and Congress has never appropriated those funds since. See?

The House of Representatives won a pivotal victory when the District Court of the District of Columbia ruled that cost-sharing reduction reimbursements without an appropriation violates the Constitution, stating, "Congress authorized reduced cost-sharing but did not appropriate monies for it, in the FY 2014 budget or since. Congress is the only source for such an appropriation, and no public money can be spent without one."

The decision did not take any immediate action to stop that spending. Instead, it may be challenged in an appeal — either to a federal court of appeals or directly to the Supreme Court.

But the House committees' investigation found that

senior administration officials drafted a legal opinion authorizing billions in cost-sharing reduction payments to the insurance industry without congressional approval. Money started flowing in 2014 and has now exceeded $3 billion. The administration has defied congressional subpoenas to supply that legal opinion for Treasury's authorization to make those payments and also issued a gag order on its current and former employees regarding the legality of the actions. The DC court has ruled, *let that be the focus, not all this Congress stuff.*

Talk about an imperial presidency! Bail to the Chief! If Congress can no longer exercise its power of the purse or its oversight responsibilities, what is the role of this co-equal branch under the Constitution?

Is this just more legal wrangling over Obamacare implementation by Republicans who never supported the program? The answer is an emphatic "NO!" for two reasons:

1. Imagine the Democratic reaction if a President Trump illegally funds the building of his wall on the Mexican border that was never authorized by Congress. (Policy ends should not justify the means because the tables can be turned. Don't worry: Trump is making Mexico pay for the wall—mucho dinero!)

2. Despite the many subsidies — legal and illegal — flowing to insurers in the exchanges, they still remain fundamentally actuarially unsound — plans pulling out, hiking premiums, etc.

Doug Badger, deputy assistant to President George W. Bush for legislative affairs, testified to the Energy & Commerce Committee about the health exchanges: "Obamacare's result is a dysfunctional 'market' that attracts high-risk enrollees and repels low-risk ones, leaving insurers with a losing proposition: a pool of customers who are disproportionately older, less well, and paying premiums that are too low to cover their medical bills. To avoid the political embarrassment of insurers withdrawing en masse from the exchanges, the administration has chosen to supply them with unlawful payments and stonewall congressional inquiries into this misconduct." Nailed it!

White's testimony at the Ways and Means Committee, argued, "Overreach by the ACA has also contributed to high and growing health insurance premiums, marked by average double-digit price increases ... CBO has estimated that the essential health benefits, actuarial value, and guaranteed issue requirements alone drive up costs by 27 to 30 percent. The median premium increase for 2017 is 19.2 percent based on average enrollment-weighted proposed rates already filed."

Just as troubling, much of the increased coverage in Medicaid and the exchanges appears to have been diverted from the employer market. Two days after the president took his victory lap in JAMA, his Health and Human Services Department quietly released data showing an alarming decline in the number of small businesses offering health insurance coverage since enactment of ACA. The offer rate of health insurance for businesses with fewer than 50 employees dropped to below 30 percent for the first time in 2015. Six years ago, when the ACA was passed, 39 percent of small businesses offered health insurance. Businesses with fewer than 50 employees:

- 29 percent offer rate in 2015
- 32 percent offer rate in 2014
- 39 percent offer rate in 2010

REPUBLICAN ALTERNATIVE?

What should be done and where are Republican solutions?

After several years of being roundly criticized for failing to produce a consensus alternative to Obamacare, in June, Speaker of the House, Paul Ryan, issued a blueprint called *A Better Way* that included a comprehensive approach to repeal and replace Obamacare. The product was a result of rank-and-file House Republican deliberations and contributions.

Under the proposal, Obamacare taxes and subsidies would be repealed. A refundable tax credit available to all would replace income-based premium subsidies. Individuals could purchase insurance across state lines and without the costly benefit mandates in Obamacare. The 40 percent "Cadillac-tax" on premiums for high costs would be replaced with a cap on the exclusion for employer-provided health insurance. Health savings accounts and other consumer-directed accounts would be expanded.

Most Medicare cuts would remain in place, as would the changes to Part D – the gradual closing of the coverage gap and the 50 percent manufacturer discount for those costs. But the proposal would move Medicare to a more competitive delivery model for new beneficiaries, known as "premium support" and gradually raise the eligibility age to match Social Security.

While the proposal remains a blueprint, it provides a clear alternative to the current path that a President Clinton would double down upon. It also provides a vital policy framework for approaching health issues that appear to be wholly lacking in the Trump campaign. 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.

The Constant Search For More Efficient Paths To Approval

STEVEN J. MENTO, PH.D.

There are several general principles that can help accelerate clinical development, beginning and ending with a focus on getting the drug to the patients that need it.

CHOOSING THE RIGHT PATIENT POPULATION

One major obstacle in clinical development is that the requirements of the drug approval process can only approximate the actual practice of medicine. Researchers usually are trying to determine if results observed in a specific model — often a preclinical laboratory model with a genetically defined mouse — can be duplicated in human patients. Regulators typically want drug developers to focus on one particular category of patient. To prove efficacy, well-controlled clinical trials often are conducted in a specific subgroup of the total potentially treatable patient population. Although clearly defined inclusion criteria provide an appropriate scientific context in which to measure effectiveness of the drug, those criteria define a subgroup that may represent only a small portion of the actual patient population that a physician would typically treat. Determining how to match the controlled population of a clinical trial to the broad patient population faced by physicians is challenging.

For example, there can be various causes — alcohol, viral infections, or obesity — that lead to liver damage and cirrhosis. Although these causes, or insults, lead to similar outcomes, disease progression, prognosis, and intervention or treatment opportunities may vary with the insult. Patients who have advanced liver cirrhosis as the result of nonalcoholic steatohepatitis (NASH) represent a relatively pure patient population in which to conduct a clinical trial, but they represent only about one quarter of all the cirrhosis patients a hepatologist would see in practice. A drug developer might conduct well-controlled clinical trials in NASH cirrhosis patients leading to approval only to create a situation in which three quarters of the patients a physician would hope to treat are not included.

In oncology, as another example, not all patients with a particular cancer are diagnosed at the same stage of disease. They also may have attempted other therapies and failed, or may not have been previously treated at all. In addition, a clinical trial may require selecting a particular subset of patients based not only on stage of disease, but also on prior treatment status. In any therapeutic area, decisions have to be made to limit the scope of patients in a clinical trial from across a spectrum of disease. One useful general principle is to conduct trials in patients with more advanced stages of disease, as higher unmet medical need translates directly into shorter clinical development pathways. Patients with more advanced disease will exhibit clinically relevant progression much sooner than patients with early-stage disease. Patients treated with a drug that can delay, prevent, or reverse progression may show benefit more quickly compared with patients on placebo or standard of care.

Choosing a specific population for clinical development is an iterative process, as knowledge gained in the process will feed back into decision making. Collecting data from trials across diverse patient categories helps during discussions with regulatory authorities regarding appropriate populations for future trials and also the breadth of the drug label. Conducting initial signal-seeking studies may help identify the right development path. By conducting trials on a group that is broadly representative of what a physician would typically treat, a developer can gain information across a range of patient categories and identify subgroups for further development. For example, with liver disease, studies conducted in patients with a mix of disease etiologies — patients with alcoholic liver disease, NASH, hepatitis C, autoimmune disease affecting the liver — could identify characteristics of patient subgroups in which the effects of a drug are particularly evident. Following these relatively

“Collecting data from trials across diverse patient categories helps during discussions with regulatory authorities.”

short-term trials, the appropriate disease stage or etiology for the next step in clinical development can be more clearly defined.

CHOOSING THE RIGHT ENDPOINTS

Another approach that can streamline the pathway to approval is taking advantage of surrogate endpoints, which are indirect measurements likely to predict clinical outcomes. For example, in the early days of HIV drug development, researchers tried to prevent the disease state of AIDS. Over time, with the improvement of assays, drugs were developed to decrease viral load and improve CD4 levels. An increased CD4 level or a reduction in viral load is not in itself a measure of clinical benefit, but higher CD4 levels and lower viral loads have been established as predictive of clinical benefit, and are more convenient to measure in a clinical trial.

In recent years, authorities have opened the door to additional applications of surrogate endpoints, especially in diseases with high unmet need and limited treatment options. For example, portal hypertension (high blood pressure in the vein delivering blood into the liver) can lead to bleeding, fluid accumulation, and decline in brain function. Most physicians agree that persistent portal hypertension will lead to negative clinical consequences for the patient. Portal hypertension is a surrogate endpoint that may be suitable to support approval.

Demonstrating an effect on a surrogate endpoint rather than clinical consequences may be one way to shorten the pathway to approval. Surrogate endpoints that are not fully established may require an extension study that takes place after marketing approval to show that the changes in the surrogate endpoint translate into bona fide positive clinical outcomes. It is also prudent to reach prior agreement with regulators on appropriate surrogate endpoints for a specific indication and how those endpoints should be measured.

DISTRIBUTING RISK BY CONDUCTING MULTIPLE TRIALS

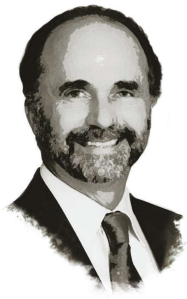
Another way to increase the likelihood of approval is to distribute risk by generating the information needed for approval across multiple small trials rather than in a single large trial. In general, demonstrating safety requires a trial with a substantially larger number of patients than a trial of sufficient size to demonstrate efficacy. However, safety data can be cumulative across multiple trials. Distribution of risk may be less important in an indication like high blood pressure, with multiple drugs available and an established development pathway. But in a higher risk area where there are no approved treatments, it may be most efficient to conduct multiple trials in parallel. Since there can be significant diversity in stage of disease and cause of a disease, it can be challenging to select the single best patient population subgroup for demonstrating efficacy. Instead, it can be advantageous to conduct multiple trials in different subgroups using different endpoints. Only one successful efficacy outcome may be needed to move forward. By conducting a series of trials, we can gather a broad, diverse patient population very relevant for safety while focusing on tightly defined patient populations and tailored efficacy endpoints in smaller trials.

A series of trials not only distributes risk but also allows exploration of potential benefits. Multiple trials may provide an understanding of a drug’s activity across a broader spectrum of patients outside of the disease category listed on the initial label. Depending on the strength of the trial data, smaller parallel trials can show similar trends and open possibilities for broadening the label.

INCLUDING THE PATIENT'S PERSPECTIVE

Developers are increasingly recognizing the importance of incorporating the patient voice in the design of clinical trials, which also can help speed development. While there may be a standard perception of the amount of risk that is appropriate in a disease area, in certain cases, patients may be willing to accept a different risk standard in order to treat their conditions. This is an important consideration in a development plan for any area. Patient quality-of-life measurements are important and should be considered as potentially relevant for any trial. There has been a recent shift among regulatory authorities to include quality-of-life measurements as a key element in the approval process, as opposed to just an aside.

Careful consideration of patient selection and patient needs, along with general strategies like distribution of risk and identification of surrogate endpoints, are all likely to help unearth the most efficient development pathway in any particular disease area. L



STEVEN J. MENTO, PH.D., president and CEO of Conatus Pharmaceuticals, has led development at numerous biotechnology firms and is a leader in the industry.

ONE On ONE With Celgene CEO MARK ALLES

ROB WRIGHT Chief Editor @RFWrightLSL

When working as a newly minted pharmaceutical sales representative, a director of purchasing at a local hospital looked at my shoes and then glanced up saying, "Those don't look like size 13s." As I was replacing someone who had been in the position for over 30 years, the hospital employee felt compelled to point out that my predecessor's success and longevity had saddled me with having some "pretty big shoes to fill." I imagine Mark Alles, Celgene's newest CEO can probably relate. Tabbed this past January to replace Bob Hugin, Alles is following in the footsteps of one pretty successful CEO. Under Hugin's watch, Celgene's revenues have grown by over 250 percent, and its stock market share price graph looks more like a Mount Everest elevation chart — only steeper!

At the 2016 BIO International Convention, Alles agreed to sit down and speak with me. And while our plans were to talk about Celgene and it being "committed to a cure," I was more curious about Alles as a person and a leader, and he did not disappoint. For example, when asked about his plans for building on the work of his predecessor, he responds, "Bob's record as CEO is outstanding, and while I'm not a legacy builder, continuity is important." Further, Alles made it clear he wasn't interested in a typical interview. "My style is to have a discussion, why don't we do that?" he shares. "When I interview with people, whether it's an investor, an attorney, or a member of the media, I expect to have a dialogue." I agree that approach is what I prefer, and so our two-way discussion begins.

FROM SCIENCE TEACHER TO MARINE

After quickly identifying that we were both from Pennsylvania and had each attended state universities

there, Alles elaborates how he was the first in his family (he is the third-oldest of seven boys) to go to college. "I wanted to go to medical school, but I grew up in a very blue-collar setting. College was expensive, and the idea of higher education as a path to what you wanted to do in life was, quite frankly, strange," he says. Nevertheless, he pursued his long-standing passion for science and, after college, became a high school teacher. That job didn't last long, though. That's because another one of his goals — to serve as an officer in the Marine Corps — drove him to go to officer candidate school at age 23.

I noted that back in 2012 when I had interviewed Hugin, he too had mentioned that he was a former Marine. "Our former CEO John Jackson also served as a Marine Corps officer," Alles adds. "I suppose there's a bit of that Marine flavor at Celgene – but not by design."

At this point, the conversation stays focused on his military service as I pepper him with questions about his experiences back then as well as what he learned as a Marine that he still uses today as an executive. His responses — respect for people, intensity, and clarity of purpose for achieving goals — don't come as a surprise. Neither does his statement about the leadership structure of the Marine Corps being very similar to the leadership structure required to run a successful business. But I am intrigued when he says having the right leadership at every level of an organization *isn't* a solution in and of itself. "You have to nurture those people and be leaders in kind," he explains. "Respect is a big part of that. For example, if somebody's job is to clean the bathrooms at night so the building is ready for the next day, well, that's an important job. If that doesn't happen, you can waste time and lose opportunities. This idea that you must stay focused on developing and establishing the best people at all levels of the organization is something I learned very early as a Marine." Alles admits that though the application of these same principles in business is not as dramatic as being ready to fight in combat, the consequences from an investor, shareholder, or patient's point of view can be similarly significant. "If you don't have a great sense of responsibility, then your organization probably doesn't have a great, sustainable culture," he states. "While corporate cultures can evolve, when placed under stress, they also can fall apart."

"SOMEDAY YOU'LL BE CEO"

Almost effortlessly, this non-interview shifts to the next logical milestone in Alles' career timeline — his entrance into the pharmaceutical industry. Again, I'm intrigued by the story, especially since it starts with his explaining that he had decided to resign from his Marine Corps commission at the same time his wife was pregnant with their first child.

His last Marine Corps assignment involved running the recruiting station in Boston, which he says had a bit of a sales type environment. "My wife actually showed me newspaper ads for pharmaceutical sales representative positions located throughout the northeastern United States," he recalls. "She knew my love for science and had already put together that joining the pharmaceutical industry should be my next move. She handed me the paper and told me I should answer the ad. But being the egotist I was at the time, I said, 'I'm a captain in the Marine Corps. Why would I go into sales?'" But Alles admits that she was right.

Soon thereafter, he took a field sales job with Miles, a division of Bayer. Over the years, he branched out beyond the commercial and marketing sides of the business. At Centocor, long before it was acquired by J&J, he was a clinical research associate, helping

The Importance Of Simplifying The Message

When speaking with many other CEOs, a consistent theme is that you can rarely over-communicate a company's vision and mission. That being said, employee understanding is often benefited by simplification of messaging. This was Celgene's approach in verbalizing its goal of being "committed to a cure."

"It is simplistic, in that it sets an ambition," shares Celgene CEO Mark Alles. "When we say we're committed to a cure, we not only think we are communicating all of what we are trying to achieve in a very straightforward and understandable way, but are asking the question, 'How ambitious are you?' In some cases, Celgene is offering therapeutic alternatives that are better for patients and not necessarily cures. Let's be clear, incremental benefit for large groups of patients is still very valuable." While incremental innovation is significant, Alles believes that if employees approach every day asking themselves what they have done to advance human health, Celgene will continue to get closer to creating cures. "Being committed to a cure galvanizes and energizes an organization across different functions," he concludes. "Sure, less than a cure can be very valuable, but that's not what we're here for."

to manage clinical trials. At Rhône-Poulenc Rorer, he worked closely with cancer chemotherapeutic agents. Recently, he's been in front of regulatory agencies with scientists all over the world, including China's FDA (cFDA), NICE (the National Institute for Health and Care Excellence), as well as regulatory officials from Brazil and Mexico.

"When I joined Celgene, my wife said that if this company ended up being successful, that I could eventually become the CEO. I told her that she was crazy. I didn't join Celgene with ambitions of becoming CEO. The fact that I am CEO is coincidental to the personal passion that I have for making a difference, which at Celgene means trying to create the world's greatest cancer and immune-inflammatory company."

Alles admits he's been fortunate to have worked with a lot of hematologists, oncologists, and infectious disease experts over the years. It's through those interactions that he developed his strong opinion that the industry is first and foremost about scientific innovation. "Sure, the world expects incremental therapies that add value, but what the world is willing to pay for is true innovation, which only can come from great science."

AN INTENTIONAL LEADERSHIP STRATEGY

Today, Celgene has 50 molecules in development, 20 trials in Phase 3, and a market cap of about $80 billion. When I ask Alles what he feels are the factors that have contributed to that success, he gives me a list of what you would expect — passion for finding cures, a risk-taking mentality, a scientific orientation, and of course, great people. That topic then morphs into a dialogue about leadership and, in particular, how Celgene has evolved. "We have intentionally had an overlap of senior leadership for more than 15 years," he explains. "There's been a thoughtful approach to having separate, yet complementary, personality traits, such as the way people think about leadership, focus on science, etc."

While many companies focus on having innovation incubators, Alles attests that the Celgene approach to innovation is best supported by having a *leadership* incubator. "We've built a very strong, sustainable leadership profile in the company," he shares. Here is what Alles means by sustainable and overlap of senior leadership. When John Jackson retired as CEO in 2006, a position he had held since 1996, he was replaced by Sol Barer, Ph.D., who had been serving as Celgene's president since 1993. When Jackson retired, he continued serving Celgene as a member of its board of directors, while Hugin took over Barer's position as president. Hugin was serving as president when Barer announced that Hugin would succeed him as CEO in 2010. Similarly, Alles was serving as president in 2016, when he was announced as Celgene's CEO. Unlike many companies where the titles of president, CEO, and chairman of the board often go hand-in-hand and tend to be held by one person, Celgene has, at times, separated these responsibilities among other members of its leadership team, a trend continued with Hugin and Alles. "I'm looking forward to continuing with Bob [Hugin] as executive chairman of the board and myself as CEO," he states. "Our board is very connected to our company and includes Jackie Fouse, former Celgene CFO who is now president and COO. This incubator of leadership and clarity of purpose [i.e., committed to a cure] keeps us very much in a virtuous cycle of focusing on what's working, and avoiding distractions," Alles concludes.

How To Pay For Cures Is A Worthy Discussion

It should come as no surprise that when faced with the opportunity to sit down with the CEO of one of our industry's hottest companies, Celgene, that the topic of drug pricing would be discussed. When broaching the subject with Celgene's Mark Alles, he states, "We are in the midst of a medical biological revolution. Thanks to the advances of science and technology, as a global society we are more advantaged today to unlock the causes and find treatments for diseases unlike any time in our history. But this also creates more pressure on a worldwide health economic system that's already heavily burdened. When you weigh the reality of world economics against the possibilities of being able to cure a cancer, or in the case of our friends at Gilead, cure hepatitis C, and then ask the system to pay, it creates a convergence of a lot of different variables and public debate." Alles believes constructive debate to be important. But patients seeking treatments, combined with the existing tensions among multiple stakeholder groups (i.e., governments, PBMs [pharmacy benefit managers], patient advocacy, and industry) make it difficult for constructive debate to happen. "Personally, I'm glad we have cures for hepatitis C, as the discussions that have taken place around the drug pricing of these products will hopefully serve as prototypes for a lot of future debates that result from future innovations. Talking about how to pay for cures is something certainly worth focusing on."

When Is Innovation Innovation?

Prior to meeting with Mark Alles during the 2016 BIO International Convention in San Francisco, I had the opportunity to meet with several members of the *Life Science Leader* magazine editorial advisory board. During the discussion (which I shared with Celgene's CEO), we debated as to when an innovation is an actual innovation. One person argued that if you don't have a commercializable product, then you probably haven't innovated anything. But if having a commercialized drug was the only criteria, would FDA-approved products (e.g., inhalable insulins) that ended up being commercial flops still be considered innovations? "These are important debates to have," Alles states. "Going back to the word commercialization – what does that mean? For Celgene it means that a therapeutic has clinical value that is recognized by regulatory agencies around the world. It also means that a market for the product probably already exists. Though we [Celgene] solve for high unmet medical need, or create an alternative to the existing standard of care, before we ever decide to go speak with a physician and try to sell the product, the need should already be there." Beyond that, in the pharmaceutical industry, drug discovery and development innovation require a threshold of evidence worthy of peer review. "For example, research on REVLIMID for multiple myeloma has been published in the *New England Journal of Medicine* [NEJM] 11 times," Alles attests. "While we can debate what commercialization means, to me, for innovation to be innovation, a product has to meet a value proposition that is waiting to be filled."

WANT TO GO **BEYOND** JUST BEING CUTTING EDGE?

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OUR PANELISTS:

MATTHEW MEYERSON, M.D., PH.D.
Professor of Pathology,
Dana-Farber Cancer Institute
and Harvard Medical School

JESSICA MEGA, M.D., MPH
CMO, Verily Life Sciences

JOHN NOSTA
Digital health influencer

KEMAL MALIK, MBBS
Top innovation officer and board
of management member, Bayer AG

JEREMY SPRINGHORN, PH.D.
Partner of corporate development,
Flagship Ventures

At the 2016 BIO International Convention in San Francisco (June 6-9), I had the opportunity to moderate an extremely impressive panel focused on how companies can create environments that go beyond being just cutting edge. Panelists included one of the world's most influential scientific minds, **Matthew Meyerson, M.D., Ph.D**, Professor of Pathology at Dana-Farber Cancer Institute and Harvard Medical School; Verily Life Sciences' (formerly Google Life Sciences) chief medical officer, **Jessica Mega, M.D., MPH**; one of the world's biggest digital health influencers, **John Nosta**; Bayer AG's top innovation officer and board of management member, **Kemal Malik, MBBS**; and partner of corporate development at Flagship Ventures, **Jeremy Springhorn, Ph.D.**, whose firm has created more than 40 companies within the VentureLabs group and has been cofounders/early backers of another 45 companies. We know that, unfortunately, not everyone can attend BIO. Further, for those who do, there are so many simultaneous educational opportunities that you often have to choose between options. In an effort to prevent discussion insights from remaining within the room at BIO's annual showcase event, *Life Science Leader* created an article to more broadly distribute the robust dialogue. What follows is an edited transcript from the *Beyond The Cutting Edge: How To Enable Life Science Organizations Today For The Societal Challenges Of Tomorrow* super session.

WHAT DOES GOING BEYOND THE CUTTING EDGE LOOK LIKE?

"When thinking about going beyond the cutting edge, what does that mean?" I asked from the stage. Describing someone in their kitchen using a sharpening stick to hone a chef's knife while preparing a family meal, it is pointed out that no matter which tool is used, a knife can only achieve a certain degree of sharpness. So how is it possible for someone to go beyond that knife's cutting edge? Here, I pointed out the existence of industrial tools (e.g., lasers, high-pressure air or liquids) that go beyond the notion of using sharpened steel to cut or shape things. This analogy set the stage for the panelists on how they go about creating environments at their organizations that encourage beyond cutting edge/innovative thinking. After the panelists briefly introduced themselves, the first question was posed, leading to the following dialogue.

HOW DO YOU DEFINE CUTTING EDGE?

MATTHEW MEYERSON: To me, cutting edge is going where nobody has gone, making discoveries nobody has

made. When I think about cutting edge, I reflect back to a conversation I had as a college student. I was at a conference where I had the opportunity to speak with some very distinguished professors. One of them said to me, "Matthew, you have to understand. People don't get any smarter. We just get new technologies. The way to do something cutting edge is to take a new technology and think about what you can do with it." At the time, I was really annoyed by this statement because I felt it wasn't true. But he was right. There are people who came before us and thought hard about the same kinds of problems. What really enable us today are incredible, new technologies. We've seen this in the computer and communications age in terms of how we handle information. We see it in genomics, with the ability to read the secrets of the genome and apply this knowledge in the making of biologics, protein therapeutics, and nucleic acid therapeutics. In chemistry, we see it with the ability to make much more complex and innovative chemical matter. All of these technological innovations are what drives our ability to do new research. We've discovered so much about cancer in the last 10 to 30 years, and today we are seeing it take root in new therapies. It's not because we're smarter or better, but because we can take advantage of new technologies that represent our collective intelligence.

JOHN NOSTA: Let me build off of that, because while I agree with you, there's one thing that is different. Abraham Lincoln once said that if you have eight hours to chop down a tree, spend six of those sharpening your axe. While this is sage advice, the thing that is different today is speed. We live in an exponential society, and the ability to pivot and move in another direction is great, but also frightening. If you look at a standard drug development protocol, it's one step at a time. I think that the cutting edge is inherently risky, because it pushes us along a path that has amazing velocity, both in magnitude and direction.

JESSICA MEGA: To follow up on that, while we have an obligation to utilize new technologies and to try to accelerate where possible, we also have to respect the biologic and life sciences pathways, which sometimes take time. So how do we be nimble and innovative and use the new technologies, while respecting the fact that biology is sometimes humbling? While we have to be cutting edge, we also have to be responsible.

KEMAL MALIK: The continuity and existence of Bayer is fundamentally important to the board of management and the supervisory board that employs us. Though Bayer has been around for 150 years, a key deliverable for the company's board is to ensure it survives at least 150 more. This is kind of different from an environment focused primarily on shareholder value. When I think about what cutting edge means for Bayer, I first considered the Oxford English Dictionary's definition — the most advanced stage of development of a thing or a process. Well, to get beyond that definition is a bit of a challenge, particularly if you're a company that is used to doing things in a certain way. But if your driving force is to make sure that you continue to exist, you are forced to look for things that can not only be disruptive to your business, but challenge your ability to continue to exist as an organization. At Bayer, we continually challenge ourselves to evolve. For example, we started as a dye company in Germany, and yet today we are a global pharmaceutical and agricultural business. Who knows what we will be in the future? For me, the cutting edge involves looking at technologies that can challenge Bayer's ability to survive.

JEREMY SPRINGHORN: The word "innovation" has evolved into a frequently used buzzword, and as things tend to go in cycles, at some point in the next couple of years it might actually become a derogatory term. There is a difference between how I thought about innovation while working at Alexion Pharmaceuticals versus how we think about working on the cutting edge at Flagship Ventures. At Alexion, innovation could be something as essential as life cycle management of a product. Incremental product innovation can be valuable to companies and patients. Being cutting edge at Flagship is a simple process that begins by asking the fundamental question, "What if?" and potentially ends with the creation of a company. Inherent in the notion of asking big "If only" questions is the need to be able to suspend disbelief about the limits of what science actually can do. This is what Google does, and there are a lot of parallels between Google and Flagship. If you believe everything you read in PubMed, your science will be constrained. There is a big difference between what people believe to be true and what is scientifically true, and the arbitrage between these is how we at Flagship create value and find cutting edge science.

NOSTA: I've never heard "suspension of disbelief" applied to the life sciences industry. That's a fascinating phrase and a valuable dynamic. When we talk about cutting edge and the influences that drive that in life sciences, it is very much company, structure, finance, and drug development. But there is also external pressure: a sense of social urgency to address big problems like diabetes, hypertension, and cancer that are pressing the issue. In response, everybody in pharma seems to be opening these new bastions of innovation, and they are called accelerators. I would argue that the acceleration of innovation is both clinically urgent and financially expedient.

MEGA: As a physician, one thing I think a lot about is how we take care of patients. We know the latest guidelines and practice evidence-based medicine. But both my parents were physicians, and they always joke that they

spent a lot of time studying worms and very little time studying the next generation of viruses and the things we tend to study today. I think people who are in the life sciences space (i.e., scientists) have always known the truth of what we are heading toward. While there has always been innovation, we've got to keep pushing. Like the previous generation of physicians, what we know of today is not enough. How do you balance this suspension of disbelief and having new ideas that really push the limits, while also testing them in a rigorous and appropriate way?

MALIK: One of the challenges and reasons large companies have accelerators is that 90 percent of what large companies need to do is sustainable and incremental innovation. I mean, it's not always "think the impossible," because if we all thought the impossible with the $4 billion Bayer spends on R&D, there's a risk we would go out of business. Our approach is to think the impossible for a small amount of money. Now, can you get the people doing their day-to-day job in R&D to also think the impossible? Probably not, and that is why we set up incubators and accelerators. Ours is called the Lifescience Center, where we focus on things like DNA editing, CRISPR, cell-based therapies, the microbiome, etc. Here is where Bayer employees can think the unthinkable, while the rest of us think about the sustainable, incremental innovation that makes up the bulk of our R&D budget. At a large organization, the challenge is having a balanced portfolio, a hurdle many small companies don't face. Perhaps small companies can always think the unthinkable, but they could also be out of business in a year as well.

SPRINGHORN: I completely agree. Innovation at a large pharma is bound by the restrictions you would expect. It has to be plannable: People have to live by objectives. It has to be efficient: People have budgets. And, it has to be predictable: You have to know what the outcomes are. While those are the constraints Big Pharma lives under, to be an innovative entrepreneur, you have to break through those things. Often, true innovation is neither plannable nor predictable, and it's certainly not efficient. Innovation at Flagship is an iterative process, almost like evolution, and similar to what Lockheed Martin did in the 1950s — Skunk Works that moved people outside the organization to allow them to think freely.

NOSTA: Evolution is a good analogy. But we find that evolutionary progress is really a punctuated equilibrium. [Stephen] Jay Gould [an American paleontologist, evolutionary biologist, and historian of science] said that innovation is not a straight line. It's these periods of wandering around, and then, all of a sudden, something happens. That punctuated equilibrium and suspension of disbelief is so interesting because of that inspiration, that magical thing that happens when you fall, you fall, you fall, and then one day you take a step forward, and then you fly.

MEYERSON: I think a big component of innovation is persistence. There's the old joke about science that if you found it the first time, you wouldn't call it research. Sometimes, when you know you're focusing on an important problem, and that that problem is going to have important implications, you just have to keep going. I'll just give an example from my lab. Back in 2001, two students of mine, Griffin Weber and Jay Shendure, developed a method to find new pathogens by DNA sequencing and comparing to the human genome. We worked on this method for 10 years and discovered nothing. But then, in that 10th year, another student, Alex Kostic, said, "Alright, I'd like to look at colon cancer." I said, "You know, you'll never find infectious agents in colon cancer. The colon's filled with bacteria." He responded, "Well, this is kind of suspension of disbelief and exactly why there could be a bacterium associated with cancer." He found one. This is a great example of being persistent and the suspension of disbelief. But another big piece of innovation is just being open to new ideas. As you're trying to solve a problem, you need to just keep trying, thinking, and looking for new ways, because there is going to be a path; it just might not be where you first envisioned.

NOSTA: I was talking with someone earlier today about measuring blood pressure, which can be done either via an in-dwelling catheter or by occluding/squeezing the artery. But now there are new methodologies looking at things like standing wave effects (e.g., Scanadu). We are also looking at red blood cell (RBC) deformation to determine its impact on blood pressure. Some of these new ways of looking at old things are interesting, because it's not half-empty or half-full perception, but a whole new perspective, and that is essential [for innovation].

MEGA: There are certain diseases we define in a way we feel comfortable. But if you think about really diving much deeper with the tools that are there, we would be redefining. For example, think about anemia in general. If we treated everyone with B-12, we would be treating a very small fraction of anemia patients. [To better treat anemia] it took the understanding of subsetting. There are many other similar examples (e.g., diabetes). For example, I'm fairly convinced that there are many subsets of diabetes. But to really understand these subtypes, we need new tools that will allow people to think about ways to intervene in a much more precise manner. New innovative technologies are providing new insights, and, as a result, we are now on the cusp of being able to say, "Let's be open to thinking about what we call a certain disease state."

Moving on, I asked another question:

BEYOND PERSISTENCE AND SUSPENSION OF DISBELIEF, WHAT ELSE ARE YOU DOING AT YOUR ORGANIZATIONS TO SPARK THE CREATIVE PROCESS?

SPRINGHORN: At Venture Labs, beyond the suspension of disbelief, we ask those fundamental questions of "If only" and "What if?" If only I had this, I would do X, Y, and Z. What if I can cure diabetes? What if I could provide a single microbiota through oral delivery and basically cure cancer? What if we could look at the microbiome of a plant seed and affect its traits in crops to help human sustainability? Asking those big "What if" questions and then suspending the disbelief that the technology is not there yet are necessary components to create a venture hypothesis. We think of the basics of these hypotheses, of asking the question of market potential, and whether or not the idea can be protected by creating intellectual property. From there you then work backwards to create technical feasibility. It might be that the technology is too early and may take a year or so to catch up. Instead of only working on the periphery of science and focusing only on the near term, being cutting edge requires asking big questions that look out to the horizon.

MALIK: At Bayer's incubator, we started with the question, "What are the societal challenges we want to be involved with (e.g., feeding the world's 9 billion or 10 billion people by the year 2050 and curing some of the big diseases)?" Then we went to the next level of iteration, such as a shortage of arable land in the world that is going to be reduced by 17 percent in the next 10 or 15 years, and we have more people. How can we end up with more efficient crop production? How can we have a world where we don't use pesticides, but perhaps use other things? How can we look at some of the monogenic disorders, and what if we could cure those? That led to the next level of iteration, gene editing, which is where we developed the deal with CRISPR Therapeutics. So we started with the societal challenges, then asked the "What if" questions, accepting that there was an enormous amount of risk attached. But then everyone began to worry about failure. This is why we set up a small Skunk Works outside of Bayer. There we want to remove that fear of failure so they can think about big things, while the rest of us can focus on the day-to-day sustainability of the company. That's the way we are trying to go beyond the cutting edge at Bayer.

MEGA: As a scientist and clinician, I often think about some early work we did (e.g., looking at genetic variance and trying to predict responses to certain drugs). We were driving in a certain direction because we had some early data. But along the journey, we were always aware that we may see something different. By being open and aware, we were actually able to steer in a direction that was spot-on. An important lesson to learn for any research team or group is that in order to put the puzzle pieces together so they make sense, you have to first lay the groundwork to make that next thing possible. If we are doing something that's important, rooted in patients and a problem that matters, then we need to put our best resources forward. We need to be creative and realize that along the way there will be insights. So let's create an environment that is conducive to that while trying to do the right thing. If you are in a research environment, and you are always willing to shut things off after three months or a year in, you will probably never learn anything. In addition, you need to be prepared for ideas to come from different places. I am continually impressed when someone approaches a well-known area of science in an orthogonal way, asking questions as to why you are thinking about something in a certain way. At Verily, we are approaching life sciences from a totally different point of view. But in addition to having a different perspective, we are also creating those intersections where you can think about things differently and allowing that to happen in a safe environment.

NOSTA: The freedom to fail is an interesting construct. Ask any Olympic athlete, Michael Jordan, or Thomas Edison. Failure defined their careers. Now, in life sciences and medicine, it's a little tricky because failure is often tantamount to bad clinical outcomes. Further, this notion of the collaborative experience defines life sciences in many ways. In the old days of pharma, it was about controlling the process and the trial (i.e., rigid, structured). But today we have the opportunity to bring in many voices, those who don't know what they don't know, engineers, biologists, and even the collective intelligence of our patient and caregiver populations. I would argue that in many instances, the patient base is smarter than the clinician. Parents with kids who have severe diseases understand the disease and the trials and have a much better understanding of the nuances of their child's condition better than any clinician. We live in a "collaboratory."

MALIK: When I joined the industry with Bristol-Myers Squibb, I was working on Plavix (clopidogrel bisulfate), and virtually all the research we did was within Bristol. When I joined Bayer in 1995, we did the same thing. Today, however, we are working with much broader groups. Xarelto (rivaroxaban), our flagship product, was developed by Jessica Mega when she was at Harvard. The world is different now, and, as a result, we partner so much more.

NOSTA: Speaking of Xarelto, one of the investigators on that product was C. Michael Gibson, who actually has

over 200,000 Twitter followers. Just think of the possible engagement. Whether you like it, it makes you nervous, or it makes you think he is a bad guy, that whole array of connectivity today is just downright freaky.

MALIK: It's hard to explain how different it is now, working in a big company, from what it was 20 years ago. We just collaborate so much more, and the collaborations are different. When I was first at Bristol, you would go to an academic center, and, in a slightly embarrassed way, you'd give them a lot of money. No one really agreed on any outcomes or what they expected to see, and then everyone was disappointed afterward. Now it's a lot more focused partnership that takes place face-to-face with what's in it for you, and what's in it for us. The collaboration component is one of the big things that is fundamentally different.

MEYERSON: I want to take off on this. We've had this collaboration between the Broad Institute of MIT and Harvard and Bayer for a while now, but I want to go back to how it started. Bayer was looking for academic partners. At the time, I had been thinking about how we had all these genomic discoveries, and I really wanted to be able to turn them into drugs that would reach patients. Then, just a real chance thing happened. I had given a lecture at the American Association for Cancer Research meeting in Delhi, India. Afterward, Chandra Ramanathan from Bayer came up to me and said, "You know, we at Bayer are interested in this field, and we'd like to talk about it. What can we do together?" It was a really different process. Bayer and the Broad Institute collectively came up with a vision of how we thought we could work together to advance cancer medicine. Similarly, our projects and ideas have evolved together. Our teams work together, both intellectually and scientifically. There may be chemists at the Broad Institute and chemists at Bayer who work together on a project, and it is a synergistic exchange of information, ideas, data, and material. What makes this collaboration so great is that we have very different styles and ways of thinking, which we maintain, yet we are able to bring them together.

MEGA: Can I follow up with that? One thing you said is to know your unique strength. What is the strength that you bring that no one else here wants to or can bring? The other is, how do you offer that while also coming up with creative models to be able to work together? I think you [Kemal Malik] were highlighting this idea that we'll sit over here and we'll put something in the middle [of the table] and see what happens. The new model is sitting side by side with collaborative partners. The piece that takes this [new model] to the next level is pressing leading technology companies to get involved in healthcare, because not doing so is doing a disservice to healthcare. The more we engage and say, "What could be more important than healthcare and improving people's lives?" the better we will be able to accelerate things in our accelerators.

WHAT HAPPENS WHEN COMPANIES FAIL TO DELIVER AS PROMISED?

At this point, an audience member directs a question to Jessica Mega about a recent article that focuses on Google's biotech venture (i.e., Verily Life Sciences) not delivering on three signature projects announced by its CEO Andrew Conrad. The questioner basically asked when nontraditional life sciences companies don't deliver on goals and timelines of bold initiatives (e.g., the creation of a futuristic device similar to Star Trek's iconic "Tricorder"), doesn't that fail to honor and respect the human biology and drug development process?

MEGA: We may all want to comment on this. To create innovative environments where these "What if" moments can take place requires inspiration, courage, and dynamic leadership. When you marry that innovative space with people who have been engineers for over a decade with scientists who understand the scientific process and put that all in a collaborative environment, that's the place where you start to make a difference. How do we create these dynamic, interesting environments and bring it together with the science itself?

SPRINGHORN: I often think about how failure is visible in the industry. In the pharma space, they have to announce clinical trial failures when a drug doesn't work or fails to get approved. That is really all the failure we hear about. There is a large amount of stuff happening daily at the bench that never sees the light of day. Personally, I applaud an executive who is willing to make a claim and state what they think is going to happen. Because, except when you absolutely have to, biopharmaceutical companies really don't show that much failure. Yet it exists and is part of the process. Failure is how we ultimately get better at what we do. I don't see that as a downside at all. At Flagship, we have created an environment that uses failure in an evolutionary sense. We have a process based on the evolution of science — essentially asking those big "What if" questions from the very beginning. We start out by doing paper research in a phase we call "explorations." That is where we try to find the bias that exists between what people and the literature believe to be true and what may actually be true. We go out to the ecosystem and talk to a lot of experts. They won't tell us if our ideas are good, but they'll tell us what is wrong with them, which is fine and part of the learning process.

Then, we do something that's very interesting, something that you usually see done with products, and that is we prototype the company. We call this phase "protoco," which is short for prototype company. We don't name the company, but assign it a title that begins with VL, for Venture Labs, and then a number. The whole purpose of the protoco phase is to ask the killer questions. This is the difference between the solo entrepreneur sitting in their garage every day, loving and caressing a single idea. The reality is they won't ask the hard question, because if it happens to be an answer they're not looking for, they'll be unemployed. At Flagship, we have money, great corporate partners, and smart people. But what we don't have is time. We look to have well-tested companies coming out of the protoco process. For those companies that survive this phase, we will fund them as a NewCo. Many people have heard of Moderna Therapeutics, a Flagship Venture company that last year was voted to be the number one Disruptor company according to CNBC's 2015 Disruptor 50 list, over many other startups including Airbnb and Uber. But that company started this process with an idea back in 2011 or perhaps even earlier, and it began with the fundamental question: Why can't you actually deliver messenger RNA as a therapeutic? At that time is was a big "What if" question. Here is an example of the bias between what was thought to be true and what is actually true. For decades, people believed that because of RNA viruses, the human immune system had evolved to a point where it was finely tuned at eliminating RNA-based products and viruses. So we looked to the literature, and it is chock-full of what RNA will and won't do. What RNAi has taught us is that you can actually change nucleotides in such a way to enable the immune system to not eliminate RNA-based structures. Nobody ever thought about actually trying to deliver a modulator in a way to give a positive effect. We asked those "What if" questions and prototyped the company within Flagship. Eventually, the company came out of stealth mode, but nobody knew about the iterative process that went into developing Moderna.

NOSTA: I'm still a fan of Google's Tricorder, and I'm just going to put a stake in the ground here and say so. The interesting thing about this whole Tricorder concept is that it carries with it psychopathology that is so intrinsic to our being. Nobody knows what a five-tesla magnet is, and no one can relate to it. But when I grew up, there was this thing called the Tricorder that I watched on Star Trek. That reality is magical. I think that some of those problems are linked to the language, because I think nanoparticle-mediated disease detection, nanoparticle early detection of an MI [myocardial infarction] that Eric Topol is doing at Scripps, is a viable concept, but those will be largely empowered by a little thing that measures it.

A question was posed to Matthew Meyerson.

WHEN YOU HAVE STUDENTS WORKING IN THE LABS AND FAILING, HOW DO YOU ALLOW THEM TO FAIL ENOUGH TO LEARN, BUT NOT SO MUCH THAT THEY GIVE UP?

MEYERSON: I've actually been thinking about the question of failure a lot. One of the most important things for people is to succeed. This is important on a level of being just one person or teams, as well as on a company level. One of the things I work hard on with students is to make sure they have a project where they are going to succeed. I always have an expectation that they will succeed on at least one project. Sometimes students might have a little portfolio of projects (i.e., low-, medium-, and high-risk). Some people are good enough that they can always succeed on high-risk projects. But for the average student or postdoc in training, they need that experience of success. Sometimes they can build a small success into a big success. For example, one of my postdocs recently published a paper on a genomic target we identified with RNAi. It was pretty simple and straightforward. Then he's taken that same approach, and he's just found something really audacious and surprising that builds on his early success. I think the ability to try something big has to be built on a foundation of success.

NOSTA: I think that is a key insight. What I tell my clients when they build their accelerators is [to be like a baseball hitter and] get on base, because senior management is going to pressure you. If you have failure after failure after failure, you can't hide behind it. It's not a home run. It's not a grand slam. Get on base, because doing so gives you that sense of confidence and provides a sense of trajectory that can help you get to a spot further out.

MALIK: Large organizations earn the right to ask the "What if" questions. If you have a track record of success in terms of doing the more routine things, you're then allowed to push the boundaries. The organization allows you to do some of the "What ifs" with 5 to 10 percent of the total R&D budget, to allow those questions to be asked. If you're an R&D organization that's consistently failed on the challenges, of course you have to report that every year during your R&D days or your investor conferences. If you're constantly failing, you don't earn the right to ask the "What ifs."

MEGA: I think that's why this concept of having a portfolio, whether it be an individual, an early-stage investor, or investigator is so important. As you are thinking about them having a portfolio, you need to also be thinking, what are some things in which we think there's a reasonable level of success? Even if it's iterative, that can still be something that is meaningful. Then, over time,

you create. Whether for an individual, lab, company, or partnerships, thinking about things via a portfolio approach and having reasonableness on what success looks like is very productive.

MALIK: That's exactly what we have at Bayer. We describe it as a "portfolio of innovation," and 90 percent of this portfolio is of the iterative and sustainable variety. But that 10 percent — don't fight without that, because, suddenly, something amazing might happen. At Bayer it is actually only 5 percent of our budget, which is still quite a lot of money (e.g., several hundred million dollars). But because the other 90 percent keeps the wheels turning, it also allows us to take a little bit of money and ask those "What if" questions.

NOSTA: Success is not like a single end point. There has to be a sense of capacity around success, because they have both financial and intellectual components. The other thing I really like about Google is it is always 10x 10x 10x. It's not incrementalism. What's that order of magnitude? What's that big idea that's going to put a one and a zero at the front of it? That's another benchmark that is elusive and tricky, but in a lot of ways I cling to that.

MEGA: It's hard, but having the freedom to think big is a real gift. There may be places where you stumble along the way, but as long as you're open to new ideas and learning, working with amazing partners and people who really care, you can make a big difference.

Another question was posed from the floor.

HOW DO YOU CREATE A SITUATION WHERE YOU HAVE INNOVATION, BUT AT THE SAME TIME MOVE FORWARD INTO DEVELOPING PRODUCTS OR TECHNOLOGIES THAT CAN BE COMMERCIALIZED?

MEYERSON: I think it's a little bit of having a range of projects. We have projects that are very early in the exploratory phase, where we're trying to say, "Here's a gene. We don't know what this gene does or how it functions." We started work many years ago – there's a disease called multiple endocrine neoplasia type 1. It's where patients get all kinds of tumors of the hormone-secreting system. We started trying to understand how this disease happens. How does it work, and what does the protein interact with? Over time, we found it interacts with a histone methyltransferase, which is important in leukemia. There was just a talk at Dana-Farber by an investigator who's actually trying to make a drug based on disrupting this protein interface. Here's something where you start with a really fundamental question, and it evolves over time. There are other examples. We did a chemical screen recently. We found a compound that looks like it could move very quickly into being a drug, and so we're trying to work with our partners at Bayer to see whether we'll be able to bring it forward and take the next step. Different people seem to get excited by different pieces of the process. A lot of moving a project forward has to do with not only having had some sort of success, but working in an area that excites you.

SPRINGHORN: I would say an area ripe for innovation is streamlining the process of getting work out of academic labs and into development and commercialization. The technology licensing offices that exist in institutions around the world know about only a fraction of the work that is actually occurring in those labs. This is particularly true because it is hard to have an up-to-date, comprehensive database of all academic research. If there was a way to have real-time, live data to know exactly what's happening in an investigator's lab for both the pharma and academic sides, that would be highly innovative and beneficial for creating new companies.

Another question was fielded from the floor, and the audience member shared how academic researchers have confided in him how much they enjoy the unique opportunity to share what they are thinking with the business side of the industry. Further, he attested to researchers on the business side of the equation expressing similar positive feelings related to communicating with academic counterparts. The question was then refined to:

DO YOU THINK THERE IS A WAY TO STIMULATE MORE FREQUENT AND OPEN DIALOGUE BETWEEN ACADEMIC AND INDUSTRY SCIENTISTS?

NOSTA: I'll give you two letters: IP (i.e., intellectual property). You always struggle with IP. But I think the nature of privacy, open sourcing, from a variety of industries, is changing the IP dynamic a little bit. I go back to that notion of the "collaboratory" as a place where some venture people can engage. We live in an era that some people refer to as the democratization of health, and the stakeholders are fundamentally changing. Patients are more active. Folks in garages are making things that are cutting edge and breakthrough. So I think the open communication forum that you are seeking is going to come, albeit with a little bit of dragging, yelling, and screaming.

MALIK: I would be interested in what Jeremy Springhorn thinks.

SPRINGHORN: Most of the IP that forms the basis of

Venture Labs companies is actually generated internally. A little-known fact is that the partnership within Flagship has over 180 issued U.S. patents. We create our own IP. In some ways you can think of us as more like an R&D organization than a venture capital firm. Academics, from Boston as well as from all around the world, come to Flagship with some great, innovative ideas. In many cases they come with only an idea or bit of science and without a management team or a business plan. But if it is a really disruptive and very fascinating technology, and if it's the kind that makes you sit up and take pause, that's the stuff that we're really interested in. In those cases we will license the IP and create the company. As such we can operate both as scientific founders and business founders, and then sometimes we are just business founders.

NOSTA: I wonder if intellectual property is something that should be protected or something that should be exposed. This is because there are so many good ideas in academia that are sitting on posters on doors of classrooms. You can expose IP and still maintain that sense of ownership. But I think a more collaborative experience where people are talking about their ideas in a broader form might be a fundamental game changer.

SPRINGHORN: It's funny you say that, because I hearken back to my early days at Alexion and business development. It was one of the greatest frustrations. Today rare disease is a hot topic that everybody seems to like. But back when Alexion was just starting out in rare diseases, it was frustrating to talk to technology licensing offices, because there was so much interesting research that would never end up getting to be the subject of a patent or anything Alexion could license. This is because most tech licensing offices were more interested in patenting research they thought would address big markets. Nobody had heard of some of the ultra-rare diseases in which some people were working, and, as a result, there were a lot of inventions that never became good intellectual property. Today, it's a little different. But I'm sure there is research occurring that doesn't ever get patent coverage due to funding constraints within the tech licensing offices.

HOW DO YOU CREATE DYNAMIC ENVIRONMENTS THAT SPARK RADICAL THINKING?

MEGA: The way we typically think about it is creating environments where you can think about problems in a different way. We create teams of people, some of whom are deeply steeped in traditional science or medicine, but perhaps bring a whole new element to this space. If you can create that environment and be comfortable with the nature that some things are going to work and some things aren't, well, that is the first step. For companies like Verily, we think about information and organizing it in a way that says, "This is going to be a simple idea of we either know something or are going to do something to make a difference." In order to make that difference, people can live on both sides. Some people can provide the knowledge with deep, new insights, which then need to be combined with people who are really interested in that area of creating new interventions. If you think about it from the "know and do" construct and how we're going to make a change, those companies that will be successful will provide, combine, and organize those insights in a certain way, then partner appropriately. Those will be the ones to lead the way in developing new and exciting types of therapies.

NOSTA: There's EQ (emotional quotient) and IQ, and I'll take IQ any day. Smart is the common denominator. Show me that electrical engineer who's just a whiz, and apply that to genomic analysis. Get them in a room, and I think sparks fly. In a traditional model, if you don't have five years of bench science, CRISPR, or genomic experience, then we're not going to let you on the team. The common denominator of brilliance applied in a synergistic environment is part of the magic.

MALIK: One of the reasons Bayer has survived 150 years is, somewhere along the way, our forefathers thought innovation was a pretty important component for our company. As you are successful, a lot of people think innovation is something that happens in R&D, and that we don't have to worry about it. We want all senior managers to realize that innovation is not only important for our company, but as a life sciences company, it is the bedrock of what we do. To that end, we systematically took the top 400 people across all disciplines (e.g., finance, R&D, marketing, commercial manufacturing) through a three-day workshop on innovation. We wanted senior leaders to think about innovation, why it's important for the company, how can we be more innovative, and how we create a culture that doesn't fear failure and is more entrepreneurial and more risk-taking.

NOSTA: A lot of clients I work with have three-day innovation summits. Basically, what they're doing is telling you to draw outside the lines, but they're making the lines via this three-day summit. There's a duality that has always bothered me. Innovation may come out of peak experience or maybe out of cognitive realities that are bigger than a methodological reality.

MALIK: I don't like the three-day methodology. What I actually like is the cathartic process of getting different people from different disciplines in the same room. This then goes down to a country level. Bayer obviously operates in 100 countries around the world. But

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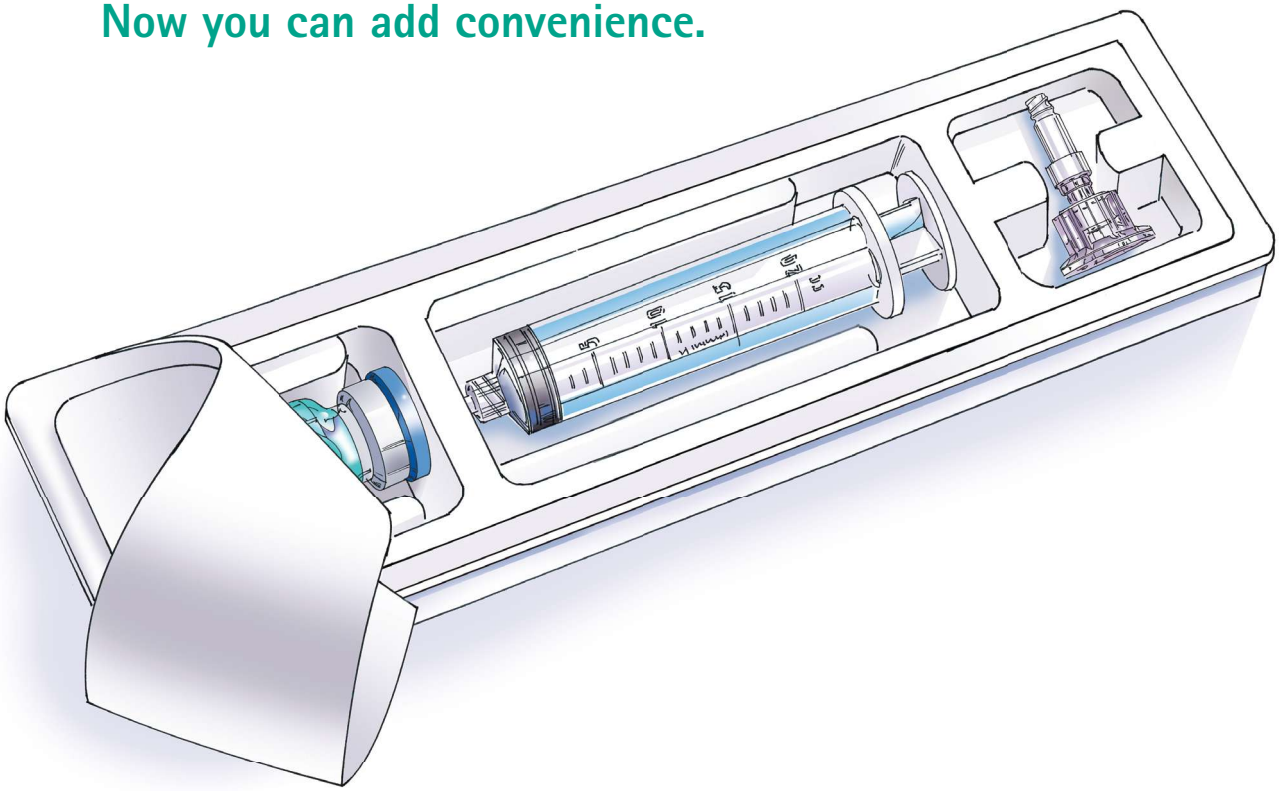

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suddenly, at a country level, multifunctional people were coming together, and a finance person was looking at this and saying, "Why didn't you try doing it like that? That's the standard financial tool we use." You get smart people, such as someone from manufacturing sharing an approach they take to a problem, or you have a chemical engineer looking at a challenge in R&D and saying, "Maybe you should try this approach." It's that cross-functional nature that is the real benefit.

NOSTA: Finding that proverbial light bulb, that "aha moment," is no less tangible. We live in the world of P values (calculated probability), but I think that sometimes the magic really is the magic, and I like that. I think maybe there are some lessons learned there, too.

MEGA: I'd be open to be that.

NOSTA: Being open to feel.

MEGA: But I think that's hard to do, as you say, in a three-day period.

MALIK: It has to be more constant. I mean, what I don't like is that we will do our normal work, then we'll be innovative for three days, and then we'll go back and do normal work. What we are trying to create is a cultural shift where the entire organization moves together.

NOSTA: Introspection, contemplation, Eastern mysticism — I think, once you open that Pandora's box of cognition, there's a lot of very interesting things, yet we often say, "Well, that's not science."

WHAT ARE YOUR PARTING PEARLS OF WISDOM?

As we concluded the BIO super session panel discussion, I asked each of the panelists to share a parting pearl of wisdom.

MEYERSON: We've been talking about novelty, openness, and collaboration. But another foundation for innovation is quality, which requires technical expertise, scientific rigor, and being able to tell true from false. Bayer, Amgen, and a couple other major pharma companies have done really famous studies of academic scientific research. Approximately speaking, the result of this research has been that 10 percent of academic science is reproducible, while 90 percent isn't. The knowledge that 10 percent is reproducible, and that we even know which 10 percent, is a remarkable testament to the scientific process. In other fields of human endeavor, maybe 1 percent is true. However, there we don't even know what the 1 percent that is reproducible is, and you just have to kind of sift through it. The ability to become reproducible and doing that thoroughly, that's an underpinning for innovation. We should never lose sight of that.

MALIK: The purpose of the session was to talk about beyond the cutting edge. I'm going to steal something that was said earlier, because I think it is really important, which is however big or small your organization is, be willing to ask that "What if" question and to think "If only." Then, be consequential and say, "How are we going to address the 'What if?'" We can address it in either a big or small way, but we can't just ignore the "What if." Think about what it could mean to your organization, and, more importantly, what it could mean for patients.

NOSTA: We are so lucky to be alive today. When I look around and see the nature of innovation, it is profound. Nothing really happened in the year 1900, though some would argue that's not true. Similarly, if you look at the year 2000, nothing happened then, either. Y2K was the thing that didn't happen. I would argue that things started to happen in the years 1915 and 1916 (e.g., the airplane, World War I, the Russian Revolution, special theory of relativity, the discovery of the mass of the electron). I believe the 21st century is beginning today, and we are at a true inflection point in human history where we will see massive changes that will result in a "hockey stick"-shaped growth curve. The next 100 years promise to bring what Ray Kurzweil says will be 20,000 years of technological advancement. A girl born today has a one-in-three chance of living to 100. We are at an inflection point in human history, and that should be celebrated in the context of research and innovation.

MEGA: I feel lucky. Three things that I've seen at the conference and that I hear today: one is that, if you put patients and people first and you work on problems that matter, your heart is in the right place. The second thing is create bold environments where we can try to make the biggest difference for the people we care about, including ourselves. The third thing is to test, iterate, accept when things do and don't work, and keep your eyes open, because sometimes the thing that will surprise you the most ultimately will have the biggest impact.

SPRINGHORN: Ask big questions and, in doing that, don't be afraid to fail, because failure is a part of the process. There are a lot of innovative things that happen in plain sight. Innovation is not a massive, complex process that has to be created. There are remarkable things that we can learn every day. The microbiome — people have known that there were bugs in the gut for a hundred years or longer. But nobody knew of that functionality how it might impact a person's overall health. There are things in plain sight that just require a little bit of knowledge and a little bit of creative thinking, and we will see huge advances that result in exponential growth. L

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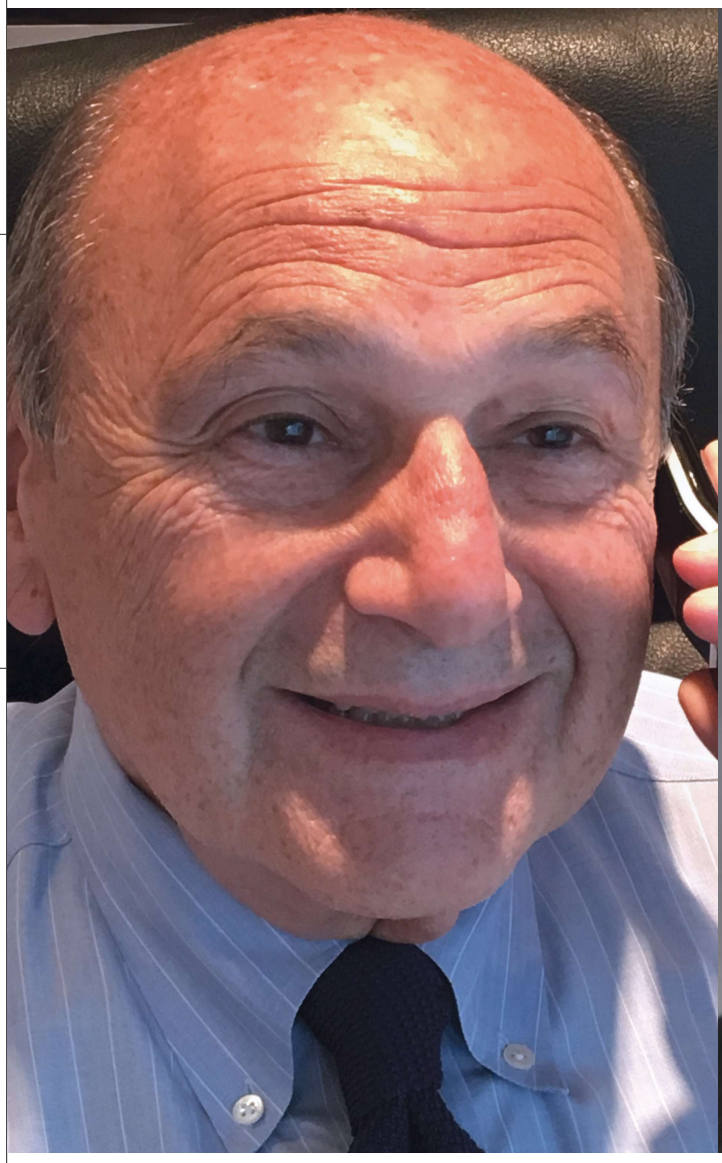

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FOCUS: Developing cannabinoid and ampakine compounds to treat multiple breathing disorders

Suffocation seldom gets the credit it deserves for causing death in so many conditions — from sleep apnea to heart failure to drug overdose. But if you view the large variety of those cases at a higher resolution, you will see "respiratory failure" as the common final, fatal effect. You don't need a pillow held over your head to suffocate; the cause can be anything, any disease or condition, that keeps your lungs from breathing adequately. How many lives could be saved by a drug that reversed respiratory suppression in its various settings? It is a long story, and we'll have to wait still longer to see its ultimate outcome, but one enterprising company, RespireRx Pharmaceuticals, appears to be making headway toward that goal.

At the BIO meeting in June, company chairman and chief scientific officer Arnold Lippa, Ph.D., told me the long history of RespireRx, known as Cortex until mid-December 2015. It is a tale of persistence, and even audacity, through repeated setbacks and recoveries. The company started up almost four decades ago atop a wave of enthusiasm for ampakines, a class of compounds that enable glutamate receptors to stimulate neural activity in the brain. At the high point of the wave, however, reverses in the field curtailed funding and a preclinical snafu derailed the company's lead development program. But the company stuck with the original idea, eventually navigating through the scientific challenges, and connected with other researchers in their area to refine the focus of the company's portfolio from broader CNS indications to neurological mechanisms in the respiratory area.

PLANTING THE FIELD

The field of neuroscience, or, as the industry prefers, CNS, has been more of a minefield than a productive plantation of new products for some time now. Since Janssen's haloperidol and Sandoz's clozapine, and with the notable exception of Prozac and the other serotonin reuptake inhibitors, whole decades have passed without the once-hoped-for advances in CNS drugs. Now, after a long string of faded startups and failed programs in the space, some analysts and investors even counsel new drug developers to avoid CNS entirely.

Against such a background, the relatively few champions in the therapeutic area, like RespireRx, stand out. Building on past failures by others and setbacks of its own, the company has survived mainly by accumulating knowledge and applying a novel idea to a combination of long-term pharmacology and cutting-edge science. And Arnold Lippa has been around to see it all — he was a part of the CNS research universe long before joining the company.

Dr. Lippa came out of the Big Pharma of the 1970s

and 1980s, where he ultimately led the molecular neurobiology group at American Cyanamid — then an industry giant that later disappeared in a chain of mergers leading to Pfizer. In 1985, as many of the big players retreated from CNS, Lippa switched to pursuing his scientific interests on the entrepreneurial business side, cofounding and comanaging the former Praxis Pharmaceuticals, followed by others over the next decade.

All the while, he also maintained strong ties with academic research in CNS as an adjunct professor at City College of New York and the NYU School of Medicine and work with the NIH and NSF (National Science Foundation). In the mid-'90s, he founded DOV Pharmaceuticals, another neuroscience development company, which he ran until 2005. He then became a principal and managing member of Aurora Capital LLC, a "small boutique merchant banking house." Yet, as he now admits, he has always preferred the science side over the business side of the industry.

From the time of Cortex's inception, Lippa had followed the company closely because of his interest in neuroscience research generally and ampakines specifically. Ampakines are compounds that enhance the actions of glutamate, the primary excitatory neurotransmitter in the brain, at one of its receptors, the AMPA receptor, thus producing electrophysiological and biochemical effects shown to improve cognition and attention deficit disorder. Cortex had focused on a particular subclass of ampakines, based on the work of Dr. Gary Lynch at UC Irvine. Lippa also knew several researchers heading a similar program at Lilly.

"Ampakines were just raging in the scientific community," he says. "Everyone thought these drugs were going to be memory enhancers, antidepressants, treatments for the cognitive problems in schizophrenia, and so on. Market caps for startups in this space were all over the place. Then the whole movement ran into a brick wall."

Scientists now know two main types of ampakines exist — high-impact and low-impact. High-impact forms can produce convulsions and neurotoxicity. With candidates in the high-impact category, Lilly shelved its entire ampakine program, which "knocked the wind out" of the space, as Lippa says. Cortex stayed in the game, becoming the leader, because it was developing low-impact ampakines. The low-impact forms did not produce the neurotoxic side effects and still showed promise in improving memory and treating attention deficit disorder.

Then, another lightning bolt struck: In tissue samples from the brains of animals treated with the company's lead ampakine, CX717, testers found tiny bubbles or vacuoles. "It was like someone had dropped an Alka-Seltzer in water and frozen it," says Lippa. "That was the death knell for ampakines."

Rather than surrender and strike the tents, however, Cortex stubbornly but quietly persisted in developing additional low-impact ampakine compounds, digging further into understanding their mechanisms and the reasons for the phenomena that had almost killed the space entirely. As it advanced other compounds, it investigated the "Alka-Seltzer effect" with CX717.

"We now have conclusive data showing that the effect is a postmortem artifact," Lippa says. "A metabolite of the drug interacts with formaldehyde, the fixative used to preserve the tissue, and the reaction is exothermic; it gives off heat, and it boils the tissue, producing gas bubbles. No vacuoles are observed unless formaldehyde is present." RespireRx now plans to publish the exculpatory data and hopes to return to the clinic with CX717 in several areas.

THICKENING THE PLOT

About the same time the company was dealing with the development setbacks — and a brush with bankruptcy — a group led by Dr. John Greer at the University of Alberta identified the presence of neurotransmitter receptors located on brain cells responsible for the central regulation of breathing in a region of the

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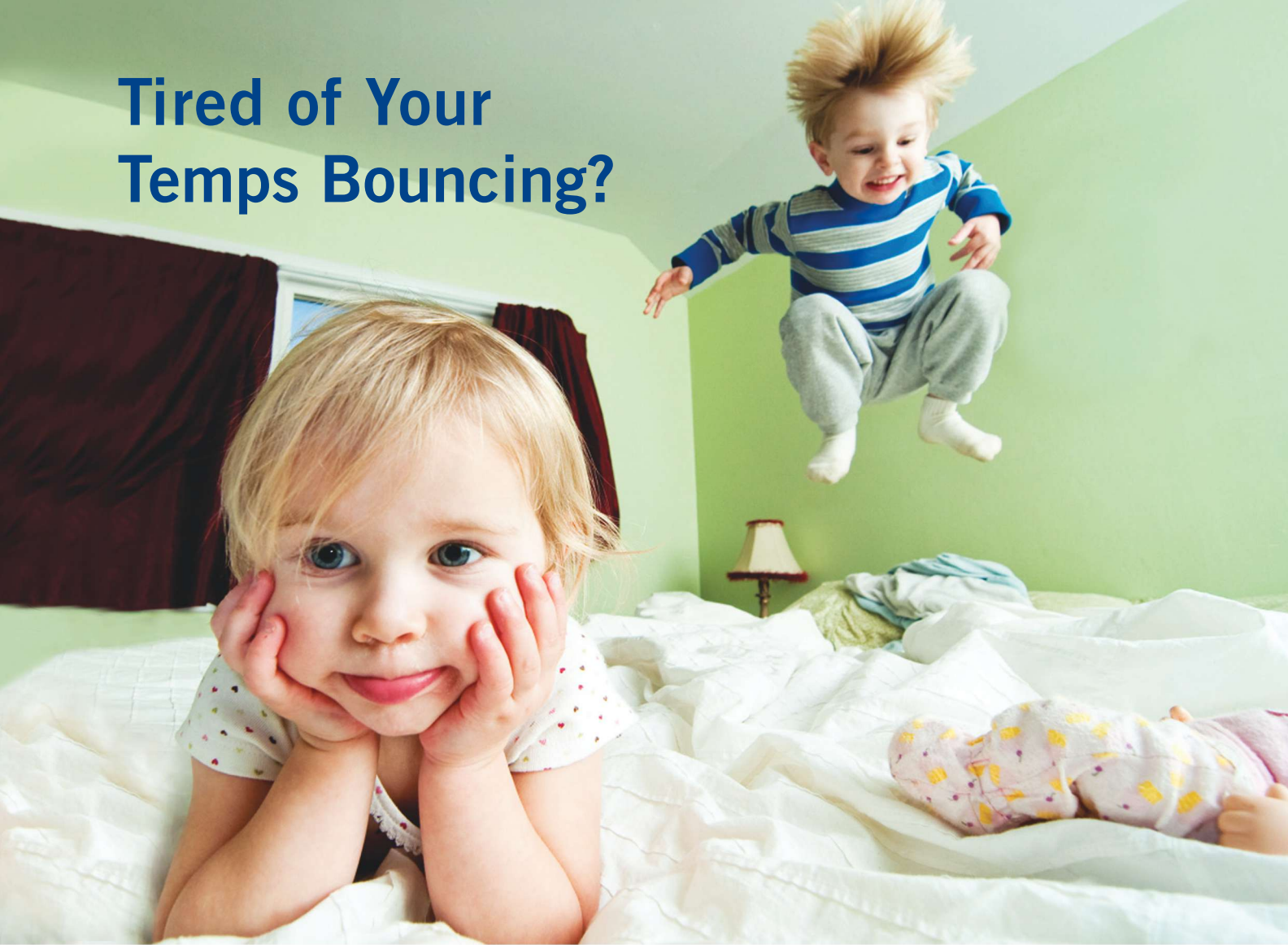

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ventral medulla called the pre-Bötzinger complex. The cells contain receptors for opiates as well as for GABA (gamma-aminobutyric acid), the main inhibitory chemical in the nervous system, whose receptors mediate the actions of drugs such as barbiturates, anesthetics, and benzodiazepines.

"Opiates activate the receptor on a cell that controls respiratory rhythm, impeding the firing of the cell, so breathing slows down, and ultimately the animals die, just like people," Lippa explains. "The same cells also contain AMPA receptors, and if you give ampakines, you can prevent or reverse the suppression, and you can measure the ampakine effect right at the level of the motor neuron. I believe it is one of the most elegant pieces of translational research ever accomplished."

The company obtained the patent rights from the research and subsequently, after working with Greer on the breathing-control insight, decided to redirect its entire portfolio into the respiratory-related CNS area. "Breathing is a lot easier to measure than depression," says Lippa. "It occurred to them — perhaps they should become a breathing company."

In 2012, the company acquired SteadySleep Rx, founded by Dr. David Carley, a leading respiratory physiologist and sleep researcher at the University of Illinois in Chicago. In an animal model of obstructive sleep apnea, Carley had shown the synthetic cannabinoid dronabinol (THC) could reverse the effects of serotonin on breathing. His company had raised funds and conducted a Phase 2a study, which showed the compound reducing sleep apnea according to the Apnea-Hypopnea Index (AHI). When the two companies merged, financing was scarce, so Lippa formed a new management team with the backing of Aurora Capital.

Lippa's team blends risk-taking experience with business and industry acumen. James Manuso, who took over as president and CEO when Lippa became the CSO in 2015, has a long history of starting, capitalizing, and running life sciences companies. Lippa's bank partner, Jeff Margolis, is also an old hand in startup financing and serves as company senior vice president, secretary, and treasurer. The chief financial officer is Robert Weingarten, who has a 30-year history in doing turnarounds. Head of R&D Richard Purcell has extensive experience in the pharmaceutical industry and has run a CRO. "None of us takes a cash salary," says Lippa. "It's the only way we could do it. We went through a nonbankruptcy reorganization. Then we got the research program off the ground, and now we're ready for the next phase — following through with clinical development."

WIDE-FIELD & CLOSE-UP

In the broadest possible view, RespireRx may focus on a wide variety of respiratory disorders, according to Lippa. "Sleep apneas, drug-induced apneas, and respiratory depression as a milder form of apnea, central respiratory problems that occur as a result of genetic disorders or injury — our drugs work in many models. For example, we have positive data for the ampakine CX717 in a mutant mouse model of Pompe disease, a muscular dystrophic condition that causes a breathing problem, and in models of spinal injury where respiratory function is also an issue. We are one of the few companies focused on respiratory physiology and pharmacology."

From a narrower perspective, the company is initially tackling two main areas of related indications — obstructive sleep apnea and central sleep apnea. Its lead product is dronabinol, now nearing the end of a Phase 2 trial in obstructive apnea. Dronabinol is an off-patent drug, approved by the FDA for the treatment of AIDS-induced and chemotherapy-induced cachexia. "Dr. Carley chose dronabinol partly because the track to development is rapid," says Lippa. "It's already approved by the FDA, so there's no long-term animal safety data to do, and we could file an abbreviated new drug application (ANDA)."

Carley recently completed dosing of 120 patients and collected the data in a Phase 2b study of dronabinol versus placebo for six weeks. "It's potentially pivotal," Lippa says. "The data is being analyzed, and later this year it will be announced."

In central sleep apnea, the company has several ampakines in preclinical to Phase 2 development to address the needs of the 11 million chronic opiate patients in the United States. According to Lippa, it is estimated that approximately half of those patients suffer from sleep-related breathing disorders, primarily central sleep apnea. Sleep-disordered breathing is considered a significant risk factor for opiate overdose, leaving about 4.5 million people at risk. In a preliminary clinical trial, CX1739, a lead ampakine, has shown potentially beneficial effects in a small group of patients with central sleep apnea.

Preclinical studies with a number of ampakines, including CX717 and CX1739, have demonstrated their ability to antagonize the respiratory depressant effects of opiates. The most commonly used opiate in these studies is fentanyl, a typical anesthesia in procedures such as colonoscopy and, more recently, appearing in

the headlines as the ultimate choice of celebrity and other pain-med users. One of the company's long-term commercial goals, says Lippa, is to develop a proprietary formulation combining a common prescription opiate with an ampakine — *a safer opiate*.

ASYMMETRIC TOLERANCE

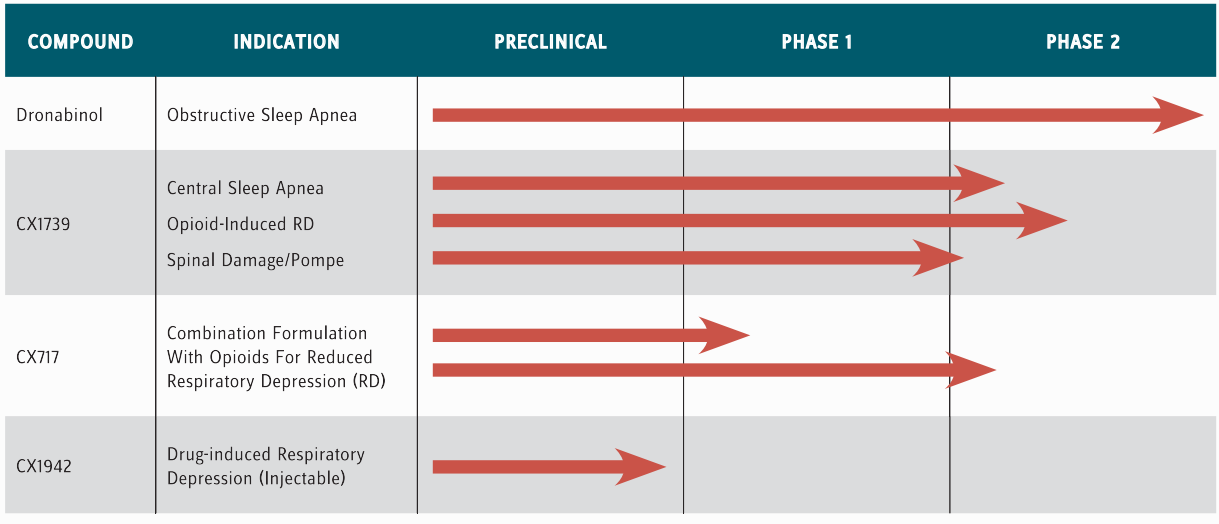
As Lippa explains, when more than 30,000 people died in the United States last year from prescription opiate overdose, it was the drugs' respiratory effect that killed them: "For patients in severe pain, an effective dose of oxycodone is 10 milligrams. You need to take 50 milligrams before you start seeing respiratory depression, but when you start taking opiates chronically, you rapidly develop tolerance. Soon the 10 milligrams doesn't work, and you go up to 20 milligrams, and after a while, 30, 40, and 50 milligrams. Tolerance develops equally to the euphorigenic effects, the so-called high, but much less tolerance develops to the respiratory depression. The 40-50 milligram dose is bumping up against the level of toxic respiratory depressive effects, and that's the deadliest problem with the opiate epidemic right now."

RespireRx has two ampakine candidates for potential opioid-ampakine combinations: CX717, assuming it can be exonerated and taken off the FDA's negative list, and CX1739. Both will go into a number of yet-to-be-determined studies, all needing additional financing. It is, to say the least, an audacious approach to the opioid dilemma — in keeping with the boldness of the company's overall thrust into the respiratory area.

"We have three primary goals: use of our products in combination with opiates, in sleep apnea, and in various orphan diseases, starting with spinal injury and Pompe," says Lippa. "In combination with opiates, there are three potential markets. One is acute and semi-acute use in a hospital or surgical setting. The second is in postsurgical analgesia, as with IV morphine, which is an easy development route because you don't need long-term animal safety. The third is chronic use in a proprietary combination."

Is this another comeback story for a waylaid technology, such as monoclonal antibodies or immuno-oncology? Will ampakines enjoy a similar renaissance, reborn in the breathing sphere? It will take further enterprise to find the answer, and the enterprise likely to make that discovery, at the end of its current development trail, now appears to be RespireRx. L

RESPIRATORY DISEASES PRODUCT PIPELINE



RespireRx

Why Proactive Risk Mgt. Is The Only Solution To The New Regulatory Reality

DAN BRETTLER AND KENNETH PIÑA

Two decades ago when the FDA suspended a pharmaceutical company's operations, it sent a shudder through the industry. While not entirely infrequent, shutdowns were widely publicized and often financially crippling, especially for middle-market firms.

While suspension in manufacturing is no less devastating today than it was 20 years ago, the number and frequency of facility shutdowns has increased at a disturbing rate despite advancements in technology, increased access to skilled labor abroad, and the growth of the quality assurance function. As a result, the FDA has sharply increased the frequency of facility inspections, and manufacturing quality control has emerged as a significant and ongoing challenge for the industry.

This new regulatory reality should cause biopharmaceutical companies to reexamine their risk infrastructures and adopt proactive approaches to risk management that will enable them to better anticipate, manage, and mitigate business interruption risks that are likely to accompany heightened regulatory scrutiny. Two valuable tools that should be included in today's biopharmaceutical risk management program are: a) a comprehensive, long-term enterprise risk management (ERM) strategy, and b) new insurance coverages that might provide a critical financial safety net when manufacturing challenges arise.

LIVING ON A FAULT LINE

Many people have met calamity due to denial. Think of the number of people who live in hurricane, flood, and earthquake zones who convince themselves that the "big event" won't happen during their lifetime. The same holds true for business leaders. Applying this notion to FDA site inspections, there recently have been a number of noteworthy "calamities" in the biopharmaceutical industry despite what were believed, at the time, to be robust internal quality and compliance initiatives.

Despite the evidence that it can and may happen, company leaders often do not spend enough time understanding the nature of their manufacturing risks (impact and likelihood) or becoming knowledgeable about insurance products that could help them effectively manage such risks. Instead, many CEOs and CFOs elect to transfer traditional risks of loss, such as physical damage of property, to their insurers, while foregoing insurance coverage for what might be one of their most material vulnerabilities — nonphysical damage loss, such as is experienced during a regulatory shutdown. Traditional property insurance policies don't address nonphysical damage losses — those that are not oriented in accidental causation in one form or another, like fire, wind, earthquake, or a mechanical breakdown of equipment.

UNDERSTANDING AND PREPARING FOR NONPHYSICAL DAMAGE LOSS

A regulatory shutdown of a key manufacturing facility or a line at such a facility can prove devastating, even catastrophic, for a biopharmaceutical company.

One of the most notable examples was the suspension of operations at Johnson & Johnson's McNeil-PPC, Inc.'s Fort Washington, PA, plant in 2011. The site was the company's primary facility for producing Tylenol and several other medicines. When the FDA took action, J&J was forced to lay off 400 workers and has spent more than $100 million on improvements over the last five years.

Moreover, as biopharmaceutical companies increasingly outsource manufacturing to foreign facilities, noncompliance identified during foreign facility inspections has become a mounting concern. In recent years, a flurry of noncompliance issues in India has

"The FDA has sharply increased the frequency of facility inspections, and manufacturing quality control has emerged as a significant and ongoing challenge for the industry."

raised red flags with the FDA, leading to increased scrutiny. The most notorious case was the U.S. Department of Justice fining New Delhi-based Ranbaxy Laboratories $500 million in 2013 for manipulating data and selling contaminated drugs. The Financial Times recently reported that there are now 39 drug-making facilities in India that have lost clearance to develop drugs for U.S. consumers due to regulatory problems.

Oftentimes, companies don't know that a third-party facility has been ruled noncompliant until months after these drugs have already been produced. But once noncompliance is discovered, it can be damaging to the finances and reputation of the manufacturer. This again leads to two important questions: a) Does your risk management program adequately and proactively identify manufacturing issues that could result in a material loss? b) If the company incurs such losses, will they be covered under the company's current insurance program?

ADOPTING A TOP-DOWN AND BOTTOM-UP APPROACH TO RISK

Considering the enormous costs associated with the shutdown of a key facility or manufacturing line, it is critical that today's biopharmaceutical management team "kick the tires hard" and make sure they truly understand the risk variables at play (e.g., revenue loss, reputational harm, civil and criminal penalties, litigation).

While most large organizations have adopted some form of an ERM program to proactively identify and manage risk events before they become catastrophes, many midsize and small biopharmaceutical companies have put in place rudimentary programs, if any at all. Yet these companies are the most vulnerable to being crippled by a manufacturing event. What many executives do not realize is that a comprehensive ERM program does not have to be expensive to be effective. A pragmatic ERM program can provide many middle-market companies with an effective method to identify and assess cross-functional risk and reduce the vulnerabilities that typically result from siloed depart-

ments, supply chain challenges, and underresourcing.

Many middle-market companies will limit their risk identification exercise to a top-down assessment, usually via questionnaires completed by senior business leaders. But today's environment demands a more in-depth assessment, one that challenges management perceptions while also merging the knowledge of senior leaders and those on the front line to develop a more realistic perspective on risk. This is a top-down, bottom-up ERM approach.

Once manufacturing risks are better understood and appreciated, the next key questions are: a) What more can the company do to further minimize or eliminate such risks? b) Will the company's current insurance program respond to these risks? c) Are there other insurance products that the company should consider that will allow it to economically transfer such risks?

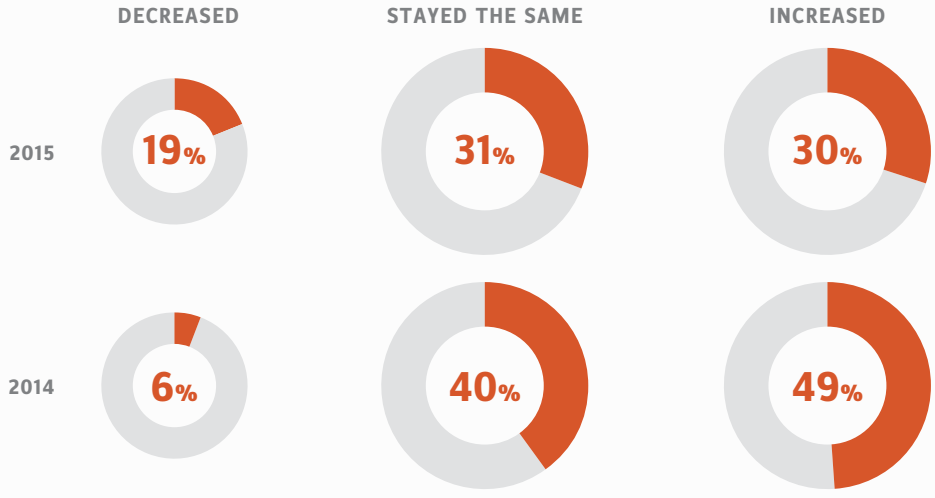
Getting buy-in and budget for a sophisticated ERM strategy and/or increased insurance coverage can be challenging. A 2015 PwC study of pharmaceutical companies reported that nearly a third saw a year-over-year increase in their compliance budget (see chart below). Yet many organizational leaders would prefer to direct compliance funds into technology initiatives and building out QA staff and procedures.

History shows that even the largest firms with significant resources experience sizable interruptions that don't involve physical damage. That's why it's crucial for risk management and compliance professionals to get their board or audit committee invested in proactive risk management. It is critical to not only take a proactive, holistic view of the organization, but to also challenge corporate management to reexamine what protections are in place should regulatory issues arise. With the backing of the board, risk managers can play an increasingly important role in protecting their company.

Significantly, the insurance industry is also attempting to proactively respond to industry needs and concerns, underwriting policies that might permit biopharmaceutical and other life sciences companies to transfer nonphysical damage losses, such as are experienced during a regulatory shutdown. For example, since fall 2015, Munich Re has offered an insurance policy that provides several unique triggers for policy coverage, including lost income from an FDA-mandated manufacturing suspension. This coverage is available for the suspension of manufacturing (at either a company's own facility or a third party's facility), product recalls, and accidental contamination, and it is specifically designed to protect earnings over the period of time dedicated to resolving the incident. Importantly, this insurance product also covers the cost of bringing in experts and resources to help manage the company through to a resolution. As this type of protection is not typically included in a traditional business interruption policy (because the event does not stem from physical damage to a facility or property), this new insurance could be an important addition to the existing insurance programs of a biopharmaceutical/life sciences company.

DAN BRETTLER is the life science practice leader at Conner Strong & Buckelew. Kenneth Piña is the managing principal for Core Risks Ltd.

Q: In the last 12 months the budget for compliance and related activities at the corporate compliance function level has...



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Identify New Revenue Streams Via Strategic Consulting Partners

CINDY DUBIN Contributing Writer

The life sciences industry is evolving and depending more on external partners, such as strategic consultants, who know what has worked well in other industries. According to the study *IDC MarketScape: Worldwide Life Science R&D Strategic Consulting Services 2016 Vendor Assessment*, strategic consulting includes high-level management consulting and advisory services, operation and process development and implementation services, and technology adoption and implementation. This is the final installment of the market intelligence group's three-part series on the topic.

This study seeks to compare major service providers with each other based on criteria important to life sciences companies when selecting a strategic consulting partner.

BROADENING THERAPEUTIC BOUNDARIES

"The historical business model for a life sciences company was to identify a new drug, run it through the process, commercialize it, and then start selling," says Alan Louie, Ph.D., research director of International Data Corp. (IDC). "Now we are saying it doesn't necessarily stop at the point of approval. Like other industries, life sciences companies are looking at working downstream from drug approval to gain additional revenue."

For example, Pfizer and IBM (one of the strategic partners highlighted in the IDC study) announced a research collaboration to develop innovative remote monitoring solutions aimed at transforming how clinicians deliver care to patients suffering from Parkinson's disease. The experimental approach will rely on a system of sensors, mobile devices, and machine learning to provide real-time, around-the-clock disease symptom data to clinicians and researchers. The ultimate goal is to obtain a better understanding of a patient's disease progression and medication response to help inform treatment decisions and clinical trial design, while also speeding the development of new therapeutic options.

"The ability to monitor the disease by measuring tremors can give us an early indication if a treatment is working and whether the disease is progressing," says Louie. "Now, Pfizer is not just looking for that next magic pill to cure the disease but instead looking at a completely new business model. An idealized outcome of that collaboration would be for Pfizer to sell drugs, monitoring devices, and services to capture the Parkinson's disease franchise and set up the company as the 'go-to' company in that field."

> *"Like other industries, life sciences companies are looking at working downstream from drug approval to gain additional revenue."*
>
> **ALAN LOUIE, PH.D.**
> International Data Corp. (IDC)

He adds, "Life sciences companies historically don't have a lot of experience figuring out new ways of expanding their boundaries. An external partner can help to advance and implement those approaches to deliver powerful benefits."

EXPLOITING TECHNOLOGY

Another powerful benefit of working with a strategic partner, according to Louie, is their knowledge of technology innovation and how to use technology to capture data that can further help with understanding a disease. The advent of electronic medical records, for instance, puts patient data together with research and clinical trial data to see what makes sense in terms of

how medical data may provide deeper insights into new drugs being investigated. Partners can help companies gain access to this information and incorporate the data into their existing processes.

"From an operational standpoint, clinical trials will likely be conducted differently based on these new data and processes," Louie says. "How do you compile all that data? Because the comprehensive data standards are not yet in place, you can easily compare apples to oranges and get the wrong answer. Effective use of technology enables you to more systematically use all available data."

According to the IDC study, with science, technology, and IT knowledge components increasingly becoming part of strategic relationships, IT service providers are also gaining traction in winning strategic consultant engagements where operational and tactical knowledge and experience are relevant. Key areas include analytics (i.e., predictive modeling) and technology adoption and implementation (e.g., mobile, cloud, Big Data, social media).

CHOOSING THE RIGHT STRATEGIC PARTNER

When narrowing down the list of prospective partners, consider the following criteria:

- breadth of the life sciences service offered and depth of industry-specific knowledge
- geographical footprint
- investment in life sciences- and/or technology-specific areas
- financial stability
- ability to accommodate different types and sizes of life sciences clients
- customer references about overall value and ability to deliver.

Louie stresses, however, that this is a partnership, which assumes that both sides bring something to the table. The consultant brings a certain skillset, and the life sciences company brings knowledge about its therapeutic focus.

Many of these partnerships revolve around strategic initiatives with a short time frame and well-defined milestones. "This helps with ROI justification," Louie says.

How BMS Is Leveraging The Patient Voice To Improve Clinical Trials

ED MISETA Chief Editor, Clinical Leader @EdClinical

The world of clinical trials can sometimes seem to be a large, corporate machine of sponsors, vendors, regulators, and sites.

However, occasionally there are moments or experiences that can drive home the point that at the heart of all clinical research are individual patients struggling to overcome serious and life-threatening diseases and individual physicians at clinical research sites devoted to helping them. Peter Ronco, VP of global clinical operations at Bristol-Myers Squibb (BMS), had one of these moments and has spent a lot of time pondering these relationships. "Over the last 12 months, one of my close family members has been a patient on a BMS oncology trial," he says. "I have directly seen what it is like to be part of a clinical trial from a patient's and caregiver's perspective — both the good and the bad. In most cases, the interaction with patients is through an investigator site. From the site's perspective, when I sat back and compared how we were actually working with some sites, I was shocked by the number of sponsor interactions that occur. I was also amazed at how complicated we seemed to be making the whole process of interacting with these institutions we considered partners."

Making clinical trial processes complicated for a site also means you're making it complicated for patients. As someone who was focused on patient-centricity, that did not sit well with Ronco, and started him on a journey to find a solution.

"We knew to compete in immuno-oncology — and to be successful — we had to fundamentally change our model," notes Ronco. "In addition to major academic oncology centers, we are also working with far more active and involved community networks and patient groups. To better serve them, we wanted to rethink the most basic aspects of our approach to these relationships."

PUTTING A NEW MODEL IN PLACE

Ronco knew that whatever procedures were put into place would need to be embedded in how the company operates and why employees come to work every day. The new program, called Aspire, has been up and running for more than a year. Prior to the launch, it took approximately nine months to develop, and involved listening to ideas from sites and patients on how to connect with them and design better studies. Ronco says, "Patient-centricity is not a new idea, and it's something BMS has been focused on for years. What we are really hoping Aspire will do is create a structure that allows us to pull together all of our efforts and accelerate them forward. Once in place, the model would simply become a key component of how everyone in clinical operations operates."

A DIFFERENT APPROACH TO PATIENT-CENTRICITY

There are two main pillars of the Aspire program, and the first involves how the company works with patients. Every company today seems to be stressing patient-centricity, but Ronco notes the approach taken by BMS is slightly different since it includes measurable outcomes.

"When study participants, caregivers, and advocacy groups hear the term patient-centricity, it can sound like a buzzword," says Ronco. "In many cases, that's exactly what it is. Patients will always question how your actions are helping them. They need to see companies taking specific, concrete actions with the interests of the patient in mind. Simply hiring a chief patient officer does not fulfill your patient-focused requirements, and misses the point entirely."

Ronco felt the first step in making patient-centricity a priority for all employees was putting the patient front and center in a very visible way. Today, if you walk into any BMS facility, you will see 20-foot high pictures of patients (as well as video screens with patient stories) placed around the entire lobby. Banners featuring patient pictures are spread across the parking lot. This effort, titled "Working Together for Patients," was designed to serve as a motivational force and a reminder to employees of why they come to work every day.

Next, BMS spoke to patients, caregivers, and advocacy groups to discover any areas in which patients needed help. Through those interactions, it was determined that

patients needed assistance understanding their disease and how they fit into the effort to find a cure. They also needed help finding the right study, getting through the trial experience, and getting back to their lives after the trials came to an end.

"We wanted patients to know they are part of a community. Participating in a trial will hopefully benefit them, but it will also benefit many others who are dealing with the same disease. Educating them on the trial process and addressing their concerns also alleviated a lot of the anxiety they had about participating in a trial."

These in-depth conversations take many forms, including patient engagement networks (PENs), focus groups and protocol prototyping sessions, meetings with advocacy groups (including board members and patients), surveys, patient conferences, and meetings with partner sites. In addition, a lot of emphasis was put on the follow-up discussions with these stakeholders to further refine and improve study designs. After all, it's common to hear of patients who completed a trial, only to never have any follow-up from the site or sponsor. Where does the drug currently stand? Was the trial a success? Did the drug get FDA approval? It seems study participants can often be the last to know.

"As part of the Aspire program, we assist patients in transitioning to the next available therapy," says Ronco. "For example, should they continue with the therapy they're on or should they be moved to another clinical trial? This approach takes patient-centricity from being a buzzword into very specific activities and actions that drive how we design and run studies."

All of those interactions also uncovered a pet peeve of many patients — the fact that they are rarely thanked for their participation in a trial. One example of how BMS addressed this was to specifically thank patients and clinical staff in its DTC advertising in the U.S. for its Opdivo medicine. Ronco states the company received positive feedback from trial participants, who appreciated being recognized for the role they played in the development process.

THE VALUE OF PATIENT NETWORKS ON TRIAL DESIGN

Ronco says the PENs, which are composed of patients, caregivers, advocacy groups, and study site personnel, are among the key ways BMS hears patient perspectives on trial designs and materials. These groups also help BMS identify any barriers to enrollment and ways to make trials easier on participants, thus improving recruitment and retention rates.

The PENs are formed early on in a development program in a new disease area, usually prior to a protocol synopsis. The timing is important, because it allows BMS to understand the potential barriers and hardships patients and their families may face, due to decisions that are made very early in the design process.

When a PEN first convenes, time is spent educating the group on the BMS clinical drug development process, the compound(s) being studied, and how they will interact in the body. This ensures all participants will understand the clinical trial process and be able to make good, informed decisions. Once everyone is comfortable with the process, there are discussions about the disease journey. All of these meetings have formal agendas, designed to stimulate a flow of ideas in both directions.

"There have been many useful outcomes from our PENs, including modifications to our inclusion/exclusion criteria, removing extra biopsies, and adding concierge services to one of our trials after learning about the hardships on the patient and the families," says Ronco. "A PEN will typically meet several times a year, both in-person and virtually, and will stay together over the life of an asset/compound. In many areas we have multiple medicines that will hopefully address a specific disease. In those cases, the PEN will cover all of those medicines."

Ronco is quick to note the PENs do not include scientists or thought leaders from BMS. Those individuals play a key role in designing the trials and protocols and determining the information that should be collected. The individuals working under the chief patient officer are generally more adept at dealing directly with patients. The groups are pulled together early on in the development process to get the patient voice involved in trial design. As Ronco notes, "Having them review a protocol after it has been developed and approved is of little value to the patient."

BMS lets the group know it will be working on a particular disease for a number of years and would like to get a good understanding of the patient journey — what it is like to have to live with the disease or to be a caregiver to a patient. One of the primary questions asked is: What must be done to help them live better lives?

"Regulators now want to know that patients value the metrics you're using to judge the success of a trial," says Ronco. "Not measuring something they deem important is also a mistake. If patients and advocacy groups are telling us that a metric is the most important measure for them, that's powerful, and that kind of input will have more influence with regulatory organizations."

DON'T OVERLOOK THE IMPORTANCE OF SITE EDUCATION

One additional component of the Aspire program relates to having better interactions with investigator sites. This effort involves several pieces. First, the site has to believe in the benefits delivered by the medicine. Sites and physicians have personal relationships with patients and will always have the best interest of the patient in mind. If they do not believe the medicine being tested will fundamentally address the unmet medical needs of patients, it will generate less interest from the site and jeopardize the study. Therefore, educating site personnel on the medicine, the trial, and the benefits for patients is crucial.

Second, there has to be an aspect of customer service that is built into every site interaction. Ronco believes interactions will be improved when sites feel they are partners with BMS, not vendors being hired to provide a services. "When you call your cable provider with a

question, you don't want to be passed around from one department to the next," says Ronco. "You want your issue to be handled quickly, efficiently, and directly. We want sites to have a similar experience with BMS."

To accomplish this customer service component, the company has invested in site-facing staff who build long-term relationships with sites and are able to address issues in a timely and effective manner. A Monitoring Excellence program has been implemented to support and grow these critical roles. Dedicated relationship managers have also been put in place to manage key site networks and academic institutions. These individuals have a deep understanding of both the BMS portfolio as well as the operations of the local sites. They are then able to resolve issues as well as establish longer-term strategies.

"We are now stressing the importance of the customer experience across all site-facing roles," says Ronco. "This is a cultural focus. We have to ensure that, regardless of which department or individual is contacted by a site, personnel will resolve the issue efficiently and directly."

Third, Ronco notes there are basic tasks that must be performed flawlessly. Here he is referring to things like having the drug and lab kits available at the right place and time and having an electronic data-capture tool that is easy to use. While these are basic steps to performing a successful trial, they are also things that will drive site personnel crazy if not done correctly. A lapse here will also impact the care of the patient. A sponsor can have the best technology available, but if it is not easy for a site to access and use, the relationship will suffer.

Once all of those basic building blocks are in place, the sponsor can start looking at ways to further improve the site experience. One example Ronco cites is a concept called "study in a box," which involves shipping all items necessary to start a patient on a trial in one convenient box. This alleviates having to ship supplies in multiple packages and expecting patients or site personnel to piece it all together. Technology also can be leveraged to scan drugs and supplies, allowing them to move through the system more quickly and efficiently.

"Today I can order a pair of shoes from Amazon.com and track the hour-by-hour progress of the shoes through the fulfillment and order process," says Ronco. "We have investigators who have scheduled patients for visits. They need to be able to track drug and study supplies in a similar way so they can run their sites effectively. One of the most frustrating things for a site is when a patient is scheduled for a visit but cannot participate in a study because of missing drug or lab supplies. Our approach is to use multiple technologies, including bar codes and Q-codes, to more effectively communicate the supply chain to sites."

EARLY SIGNS OF SUCCESS

Ronco has seen clear signs that the Aspire program is benefitting BMS, patients, and sites. From a patient standpoint, he spent some time late last year working with a PEN, and he had the opportunity to interact with a patient group for sufferers of Sjogren's syndrome, an autoimmune disease.

"We knew to compete in immuno-oncology — and to be successful — we had to fundamentally change our model."

PETER RONCO
VP of global clinical operations, Bristol-Myers Squibb

"Members of the PEN initially had minimal understanding of the clinical trial process and how they could contribute. But after spending the day with us, they came away very excited and ready to be an integral part of the team," says Ronco. "They felt we had a genuine desire to learn from them, understand them, and make a long-term commitment to them. We got a large number of thank-you notes."

BMS now performs regular site surveys across all disease areas to get insights on the experience of working with the company as well as what was done well and what could be improved. The surveys are generally five questions or fewer. Sampling approaches are used to avoid overloading any individual site. BMS also works with CRO partners to help them implement similar approaches. Site personnel are asked if they would recommend BMS to a friend or colleague and the primary reasons behind the answer. Sites that respond will be called back within 48 hours.

"If someone tells us we're doing great, that's beautiful," says Ronco. "We call them up and thank them for their comments. But more importantly, when someone says, 'Hey, your medicines are really benefitting our patients but your tools or the way you conduct your study could be improved,' that's when we get the most insight. We will immediately follow up with those sites to determine what we're doing to make their life difficult and what we can change. Determining our shortfalls and making improvements is an ongoing process."

Going forward, BMS will continue to refine the program, based on feedback received from sites and patients. Ronco notes if a new initiative, process, or technology is introduced, the first question now asked is how it will help make clinical trials better for sites and patients. L

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Taking The Guesswork Out Of Drug Development

TRISHA GLADD Life Science Connect Editor

Before a drug can reach any major milestone in development, the idea for it must first cross the "valley of death." This is the place between the lab and commercialization where good biomedical ideas often get lost and die.

One cause of this is a drought in funding to academic institutions, which, according to a recent article in *Newsweek*, is where more than half of breakthrough drugs in recent decades have been discovered. As NIH funding has decreased and the cost of conducting biomedical research has gone up, highly trained scientists with potentially groundbreaking ideas are left with no outlet to commercialize their idea.

To save great ideas from this unfortunate fate, the Harrington Project for Discovery & Development created a bipartite collaboration leveraging both nonprofit and for-profit organizations: Harrington Discovery Institute at University Hospitals in Cleveland, OH, with its Innovation Support Center (ISC) and BioMotiv. The Harrington Discovery Institute, the nonprofit arm of the project, is led by Dr. Jonathan Stamler. It supports physician-scientists who want to improve patient care through the development of new medications. To drive this effort, the institute created the Harrington Scholar-Innovator Program in 2013, which distributes up to 12 Harrington-Scholar Innovator Awards to early-stage innovators whose research has the potential to change modern medicine. Applicants' ideas are reviewed by the institute's scientific advisory board, and those with a potential for commercial success are awarded. Initially, each applicant is given $100,000 but has an opportunity to qualify for up to $700,000 over the course of the program, which is two years. While the financial support provided is modest compared to the total cost of bringing a drug to market, it can make a considerable difference when a scholar is seeking resources to bring an idea from the research phase to an attractive package for commercial purposes.

CONNECTING GREAT IDEAS WITH GREAT MINDS

Once selected for the program, the new Harrington Scholars (as they are referred to) are paired with a coordinator from the ISC, which is composed of an advisory panel of leading experts in drug development. As an example of the expertise available to scholars, Dr. Perry Molinoff, chairman of the ISC's advisory panel, has more than 30 years of experience in both the academic and industrial sectors. He is currently a professor of pharmacology at the University of Pennsylvania and has served as the executive VP of R&D at Palatin Technologies and VP of neuroscience and genitourinary drug discovery at Bristol-Myers Squibb Pharmaceutical Research Institute. Dr. Molinoff is joined by 15 other board members who have served in positions like VP and chief scientific officer at some of pharma's biggest names, such as Pfizer, J&J, AZ, and AbbVie. Collectively, the panel has played a role in the development of over 100 approved drugs on the market.

The scholar and advisor are paired based on which board member's expertise is the best match for the project. If necessary, a coordinator can call on any one of the other panel members, depending on what the project needs. For example, a coordinator with knowledge in medicinal chemistry may initially be paired with the scholar, but as the project progresses, they may call on a formulation expert or someone who has expertise in preclinical models. Monthly meetings are conducted between the scholar and their team, where they will create and execute a plan that ultimately generates interest in the drug from pharmaceutical companies.

"There are ideas for new therapies that have floundered because there was some safety flag raised, or there was reluctance on the part of the FDA to allow the new therapy to go through," says Diana Wetmore, director of the ISC. "In academia, these scholars often do not have access to this in-house knowledge and are only looking at what's really appealing from a scientific perspective and what new information they could publish that would be interesting in that particular field. They are not thinking necessarily about things like the best intellectual property coverage they'd need to put in place before publishing their findings, what happened with other potential new therapies in this field that have failed, and what experiments they would need to do to demonstrate that their idea overcomes that challenge. This is the kind of input the advisors can bring to the table, considering they have had careers in the pharma industry and, therefore, have that inside knowledge."

"In academia, these scholars often do not have access to this in-house knowledge and are only looking at what's really appealing from a scientific perspective."

DIANA WETMORE
Director, Innovation Support Center

Through this program, the risk of failure is reduced by helping deepen the package of information to support the scholars' concepts, thereby moving more great ideas toward a successful launch.

CLOSING THE VALLEY OF DEATH

Beyond philanthropic contributions from the Harrington family and a portion of funds from The University Hospitals of Cleveland, OH, the Harrington Discovery Institute receives financial support via donations from a number of sources and leverages its support for additional scholars through foundation partners. These partners include the Alzheimer's Drug Discovery Foundation, the Foundation Fighting Blindness, and the University of Oxford, which launched the Oxford-Harrington Scholarship Programme to support clinician researchers in 2014. Each program aims to achieve the same goal – provide support to researchers working on novel drug discovery initiatives that have demonstrated a potential for commercial success.

The Harrington Project also includes a for-profit arm, BioMotiv, which is an early-stage incubator-style discovery company. It helps early projects progress down the drug development road and then partners them with pharma. In July 2015, BioMotiv announced the formation of Sujana Biotech, LLC, which develops novel technologies and therapeutic products for a range of inflammatory and vascular disorders. This technology is based on research from scientific founders and graduate scholars of the Harrington Scholar-Innovator Program. It is one of five successful projects from the program that have been or are actively engaged in licensing agreements.

Scholars also can take their ideas outside of the institute. One unique detail about the program is that all IP that results from the guidance of the ISC advisors belongs to the scholar and the scholar's institution. "We take no stake in it," says Wetmore. "We just want to see these projects move forward and new medicines become approved." She also explains the benefits this kind of program offers pharmaceutical companies seeking new therapies to pursue. "If you are a pharma company or an early-stage development company thinking about the statistics of failure, and you're comparing something that has been through our program to something that was developed inside an academic institution only, then what we hope is that our success rate down the road is going to exceed the success rate of an unguided academic cohort."

Jean Y. Tang, M.D., Ph.D., associate professor in the department of dermatology at Stanford University and graduate scholar from the Harrington Scholar-Innovator Program, presented at the 2015 Harrington Scientific Symposium about her experience with the program and what it taught her. Dr. Tang studies basal cell carcinoma, which is the most common cancer affecting 3 million people each year. The only form of prevention is sunscreen, and the only current form of treatment is surgery, which often leaves patients scarred and disfigured. Before working with the advisors from the ISC, Dr. Tang says her approach to commercializing her idea would've just been "try it in patients." When presenting to pharma companies, she said she would often present a very technical slideshow, likely losing her audience halfway through. Through the guidance and knowledge of the advisors, she and her team now understand what information generates interest from pharma companies and how it should be presented in order to have a chance at commercialization. "We now know to ask the critical question," she explains. "What is the right clinical indication for this topical anti-BCC (basal cell carcinoma) product? Is it in prevention? Is it in treatment? The amount of data and the kind of clinical trials are different for each of these indications. What's the competition? What's the standard of care? Where is your unmet need so that our product, after all this hard work, is commercially viable? These are the things as physician-scientists, through all of our rigorous training and research, we were not taught."

Dr. Tang says they hope to develop a topical treatment without the systemic side effects that, because of the large unmet need, is estimated to have a $500 million to $1 billion market revenue. Since her August 2015 presentation, Dr. Tang has successfully filed an IND (investigational new drug) for the treatment and enrolled her first patients in clinical trials. She says working with the ISC taught her the language of the industry and gave her the guidance to eventually get to Phase 1 proof-of-concept trials. "That is the major evaluation and a value inflection point for a biotech startup. Pharma companies really want to see data in humans. Once you have that, the valley of death closes." She continues, "We have found, as physician-scientists, the Harrington Scholar-Innovator Program has renewed our courage and our fortitude to do what we have always dreamed of and trained for. Because of their excitement, it has renewed ours."

Executive Well-Being – Body, Mind, And Purpose

MIM SENFT

Your team looks to you for more than just leadership related to getting the job done. How you treat yourself, how you communicate with others, and the actions you take influence everyone around you. That means you have the opportunity to positively influence the health and well-being of your team. That's good for you, your team, and your company.

BODY

There is no doubt that physically taking care of yourself can help you be a better leader. That doesn't mean you have to be a marathon runner or a high-level yogi. Taking short breaks, holding walking meetings with your team members, and participating in an on-site physical activity can help influence those around you to get more active and help you feel better. It is also good for business.

More movement and less sitting have real benefits in the workplace:

- It boosts oxygen levels in the brain, which helps increase focus
- Moving allows your brain to view problems in a different way
- Your immune system works more efficiently, keeping you healthier

MIND

Most of us are on information overload. We are all receiving thousands of pieces of information on a weekly basis. It's important to know how to cut through the "noise." Mindful leadership means being better at understanding whether an issue is one more fire drill, or whether it can have a larger impact on company goals.

Mindful leaders are more likely to:

- Have a deeper understanding of their own strengths and challenges
- Better manage stress
- Understand what motivates different team members, to better utilize talent

These are just some of the reasons why MBA programs at universities like Harvard and Wharton are including classes that incorporate mindfulness and leadership. The scientific research on mindfulness shows that learning how to be more mindful can help better regulate emotional responses and increase the capacity to be a better creative problem-solver.

PURPOSE

We know that being physically and mentally at our best is good for business. But without a connection to purpose, we miss out on maximizing our own, and the team's, potential. The research is clear that employees are more productive when connected to purpose.

Helping your team connect to purpose might be:

- Making sure you understand what purpose means to your team and showing them how that connects to the company
- Your team working together to give back to the community
- Younger workers mentoring older workers to help them better utilize technology and older workers mentoring younger workers to better understand the company culture and goals

As a leader, your time is very valuable. When you understand your own connection to body, mind, and purpose, and being a visible model, you and your team will be at your best. L

MIM SENFT is president and CEO of Motivity Partnerships. She has over 20 years of corporate experience in project management, benefits design, and wellness program strategy. She specializes in providing companies with strategies that positively impact culture and create team innovation.

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