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OCTOBER 2017

# Can David Hung Lead Axovant To Alzheimer's Success?

p. 16

DAVID HUNG, M.D.
CEO, Axovant Sciences

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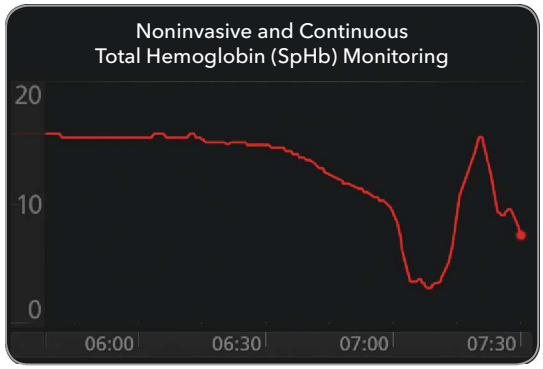


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[1] Ehrenfeld et al. *J Blood Disorders Transf.* 2014. 5:9.

[2] Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4.

Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN-S Hematology Analyzer.



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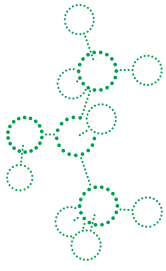

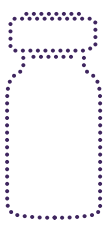

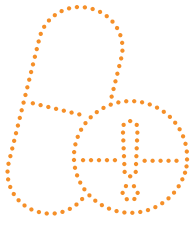

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**LIFE SCIENCE LEADER** (ISSN: 21610800) Vol. 9, No. 10 is published monthly by Jameson Publishing, Inc. at Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. Phone (814) 897-9000, Fax (814) 899-5587. Periodical postage paid at Erie, PA 16510 and additional mailing offices.  **SUBSCRIPTION RATES** For U.S. based subscribers, $295 for one year. If your mailing address is outside the U.S. the subscription price is $445 for one year. **POSTMASTER:** Send address corrections (Form 3579) to Life Science Leader, Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. **PUBLICATIONS AGREEMENT:** No. 40722524 c/o AIM, 7289 Torbram Road, Mississauga, ON L4T 1G8.

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# In Need Of A Biopharma Bright Spot?

**ROB WRIGHT** Chief Editor

This past summer, a friend told me he had taken a "summer vacation" from the national and local news, noting, "It's been awesome being totally stress free." There is some wisdom in his words. Some psychologists suggest that exposure to negative and violent media may have serious and long-lasting psychological effects beyond simple feelings of pessimism or disapproval and can actually exacerbate or contribute to the development of stress, anxiety, depression, and even PTSD. That's not good news for an industry such as ours that is constantly under public scrutiny.

One of the few national news bright spots happened mostly in the dark (i.e., the positive coverage of the total solar eclipse). But doesn't that now seem like a distant memory? If you are anything like me, you are probably in need of a little more positivity. And despite what many mass media outlets might lead you to believe, the biopharmaceutical industry has a plethora of bright spots. For example, last month we featured Brent Saunders, who shared the inside scoop behind the speedy development and publication of Allergan's social contract with patients. We continue this month on this optimistic theme with another bright spot — Axovant Sciences CEO David Hung, M.D.

A highly trained physician, Hung's decision to leave his academic practice of medicine and join our industry was driven by tragedy — the death of a 28-year-old patient. Like so many entrepreneurs who find themselves founding biopharmas, Hung wanted to make a difference beyond what could be done treating one patient at a time. There are those who choose to focus on the fact that the first company Hung founded, Medivation, failed in its quest to successfully develop a treatment for Alzheimer's disease. What is lost with that kind of myopic view is all the good Hung has done beyond just the successful development of XTANDI (enzalutamide) for the treatment of metastatic, castration-resistant prostate cancer.

In June I had the opportunity to interview Hung in person during BIO, and to say it was a delight would be understating my experience. Because despite the failure of Dimebon (the drug Medivation had been trying to develop for Alzheimer's), which we talked about at length, the man continues to ooze positive energy. His infectious smile and contagious enthusiasm made the article so much fun to write that, upon completion, I did something I had never done before — I put together a list of my top 10 quotes from the discussion, which were published on my chief editor's blog on Aug. 22, 2017. Not long after, I was pleasantly surprised when a reader paid it forward by sharing the following, "I worked for David, and there is nobody better at leading people from top to bottom." We hope you enjoy our conscientious decision to focus on the positive aspects of our industry. For I prefer Thomas Edison's perception of failure — "I have not failed. I've just found 10,000 ways that won't work."

Life Science Leader

OCTOBER 2017 VOL. 9 NO. 10

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## Q What are your thoughts on the new FDA Commissioner's ( Scott Gottlieb) proposal to make generic drug approval easier, and do you agree that the impact will be a lowering of drug pricing?

**A EVIDENCE SHOWS THAT MORE GENERIC COMPETITION** leads to lower costs. One FDA analysis found that when there are three or more generics on the market, prices fall by more than half relative to having only one generic available. Thoughtful consideration of how to remove unnecessary regulatory barriers, as Commissioner Gottlieb has proposed, is an important step toward a more competitive generic marketplace.

But it is vital that any steps taken by the FDA to speed generic entry maintain the important patient safety safeguards that have made FDA approval the world's "gold standard" for safety and efficacy. Poor first-cycle generic approval rates are one of the biggest barriers to speedier generic entry.

**TOM DILENGE**
is president, advocacy, law & public policy division for the Biotechnology Innovation Organization (BIO)

## Q What's next in processes and facilities?

**A ON THE PROCESS SIDE**, single-use technologies are rapidly being implemented, especially in bioprocesses. This can be seen in the growth rates of single-use suppliers and new bioprocessing sites that chose to implement single-use process equipment (when the volume range allows it). This process technology functions as an enabler for new facility designs, for example, creating cleanroom islands surrounded by media and buffer supplies within a larger open area.

The future for processes and facilities holds a higher degree of standardization as well as platform designs that can be deployed within months. Today's capacity needs and increased competitive pressure make many legacy systems obsolete, creating the need for more outside-the-box mind-sets.

**MAIK JORNITZ**
Maik Jornitz is CEO of G-CON Manufacturing and founder of BioProcess Resources. He has more than 30 years of experience.

## Q What are you doing to address some of the common challenges confronting the industry (e.g., industry image, clamor for government intervention)?

**A ALL INDUSTRIES HAVE A RESPONSIBILITY** to respond to public concern about environmental sustainability. As an advocate for single-use technologies (SUT) in biologics and sterile-product manufacturing, I see the need to address both the perceptions and the reality of the waste disposal challenges presented by SUT. Life cycle analyses of single-use technology vs. conventional reusable equipment consistently show that the overall environmental impact of SUT is positive. However, users are often unaware of the benefits provided by reduced water and energy use. Common questions are "What do I do with these used parts?" and "Isn't this bad for the environment?" To address these legitimate concerns, to promote a broader understanding of the environmental positives of SUT, and to publicize the sustainability-related efforts of suppliers and biopharmaceutical manufacturers, we have formed a Sustainability Committee within the Bio-Process Systems Alliance (BPSA).

**MARK A. PETRICH, PH.D., PE**
is director, single-use systems engineering at Merck. He serves as second vice chair of the Bio-Process Systems Alliance.

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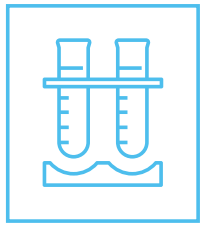
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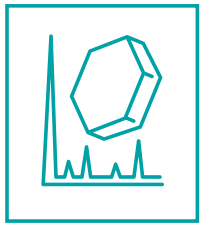
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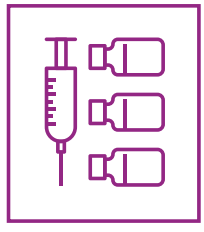
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# What Does The Trump Pivot **Mean For Healthcare?**

**JOHN MCMANUS** The McManus Group

Frustrated with congressional Republican inaction on major pieces of his agenda, President Trump cut deals with Democrats on a short-term increase in the debt ceiling and funding the government. Then, to the surprise and consternation of his base, in a dinner with Senate Minority Leader Chuck Schumer (D-NY) and House Minority Leader Nancy Pelosi (D-CA), Trump agreed to work on a deal to extend the Deferred Action for Childhood Arrivals (DACA), a Democratic priority.

But what does Trump's new interest in working with Democrats mean for healthcare policy making? That is not yet clear.

The final straw for Trump was failure of the Senate to repeal and replace Obamacare in August. Two days after Senator John McCain (R-AZ) — newly diagnosed with brain cancer — made a dramatic appearance on the Senate floor to vote for a motion to proceed on repealing and replacing Obamacare, he joined two other Republicans and a unified Democratic Senate to scuttle the bill Majority Leader Mitch McConnell (R-KY) had fashioned to repeal major elements of Obamacare. To the shock of the GOP establishment, President Trump proceeded to ridicule the Republican leader in a tweet storm usually reserved for Democrats and political enemies.

The debt ceiling deal was made over objections of the bicameral Republican leadership. Speaker Paul Ryan (R-WI) had blasted the notion of a three-month extension as "ridiculous" just hours before the bicameral leadership meeting with the President, where Trump appeared to make the decision on the spot. In doing so, President Trump overruled his own Treasury Secretary's position for a longer-term solution.

These moves show that President Trump will not be tethered to the Republican Party or even his own administration's positions if he sees opportunities to make deals. That new reality has caused hand-wringing on two major issues that will dominate the rest of the year: tax reform and what to do about the imploding of Obamacare. Members of Congress and seasoned Washington veterans alike find themselves in uncharted territory, wondering how to deal with a President that now appears to have abandoned policy and political principles that have guided legislating for decades.

## DISPOSITION OF OBAMACARE UNCERTAIN, BUT ACTION ON OTHER HEALTH ISSUES PROGRESSES

Following the cataclysmic implosion of the Senate bill, the Senate Health Education Labor and Pensions (HELP) Committee held a series of hearings in an attempt to build bipartisan consensus primarily on shoring up the individual market. After the fourth hearing, Chairman Lamar Alexander (R-TN) said he thought there were three areas of consensus: Congress should approve temporary funding for cost-sharing reduction payments, allow those 30 and older to purchase catastrophic "copper" plans, and give states more flexibility regarding insurance plan design. But Democrats have not signaled whether this will be enough to gain their support. More importantly, such a deal skirts the thornier issues of ending the Medicaid

expansion, repealing the individual mandate, and the slew of healthcare taxes that are a priority for most Republicans and outside the HELP jurisdiction.

Meanwhile, Senator Bill Cassidy (R-LA) — a former physician and energetic lawmaker in his freshman term — joined Senator Lindsay Graham (R-SC) to craft one last Republican attempt at repealing and replacing Obamacare. The bill would repeal the individual mandate and medical device tax but leave the pharmaceutical fee and many other Obamacare taxes in place.

The heart of the bill is a block grant formula that would give each state a set amount of money to spend on their own healthcare programs, based on how much they would receive under Obamacare. The states would be provided enormous discretion on how those funds would be spent and could decide to retain, modify, or repeal the Obamacare mandates.

That bill's formula is complex, and white-shoe law firms are still unpacking the policy ramifications. But the overall result would be less federal spending than under Obamacare, with a redistribution of the funding from states that expanded Medicaid to states that chose not to. All funding would stop in 2026 and would require a subsequent act of Congress for continued flow of funds, raising the ire of Democrats.

It must be voted on before September 30 when the current budget resolution expires, and Cassidy believes he is within a vote or two from passage. McCain, a close ally of Graham, could come on board, but apparently Senator Rand Paul (R-KY), with a libertarian view of healthcare, is unhappy with the product. Such a result would still leave them short of the 50 votes needed.

In any case, the HELP and Cassidy-Graham bills appear markedly different from the Republican repeal-and-replace bill passed by the House earlier this year. Final resolution of a bill getting to the President's desk still looks like a long shot.

But beneath the partisan rancor and public scrutiny of Obamacare's fate, the committees of jurisdiction are constructively advancing bipartisan legislation to fund and operate key healthcare programs:

- In July, President Trump signed legislation to reauthorize the FDA and its manufacturer user fees for five years so that drug and device applications could be reviewed in a timely manner.
- In September, Finance Committee Chairman Hatch (R-UT) and Ranking Member Wyden (R-OR) announced an agreement to fund the Children's Health Insurance Program (CHIP) for five years. That bill must still move through the legislative process, and the House seems focused on a two-year package, but the issues appear resolvable.
- The House Ways and Means and Energy & Commerce Committees are advancing a series of bipartisan, targeted Medicare bills dealing with everything from prostate cancer misdiagnosis and caps on therapy payments to ambulance payment reform.

The pharmaceutical industry is gearing up for an end-of-year deal on CHIP and these Medicare issues that could call for resources from the industry. The industry has been successful in recent years in blocking pharmaceutical-focused offsets. But that success has generated the irritation of congressional committees tasked with fashioning these packages and securing offsets from various industries.

The committees are currently contemplating several measures that could negatively impact the pharmaceutical industry, including proposals:

- to encourage speedier generic entry by ending "pay-for-delay" and requiring manufacturers of products with Risk Evaluation Mitigation Strategies (REMs) designations from the FDA to share product for necessary bioequivalency testing
- to encourage greater generic substitution by low-income Medicare beneficiaries by raising brand-name copays and/or lowering generic copays
- to reduce payments for physician-administered Part B drugs
- to increase Medicaid rebates on certain "line extensions" of brand-name drugs.

The wild card in all of this is President Trump himself. Was this a carefully calculated move to shake up the Republican establishment or another symptom of Trump's erratic and impulsive approach? Only time will tell, but the playing field is now open for other deals, and everyone (Republican or Democrat) must proceed with caution lest they be caught unawares.

What will he demand? Will he side with an emboldened Democratic minority on pharmaceutical pricing issues? Good questions with no clear answers. 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.

# How Moving Up Through The Ranks Can Shape A Biotech CEO

JOHN MASLOWSKI

All CEOs of small, publicly traded biotechs (those with 50 employees or less) are required to wear many hats in the office every day. That's why I believe that having a leader with a diverse background and experience in a variety of functional areas is an asset that can help guide a company to meeting its milestones. Let's look at some of the various areas of expertise that can help create a more diverse C-suite executive.

## QUALITY ASSURANCE

Working in quality assurance (QA) during an earlier phase in my career taught me how a background in this area can be advantageous to biotech CEOs. It helps, for example, when a company is mapping its product development strategies, leading up to a potential FDA approval and the processes supporting it. Specifically, this can involve advising on such areas as auditing and cleanroom design and in optimizing and scaling up the manufacturing process in anticipation of commercialization of a drug. Oftentimes, the challenge involves ensuring goals are met within strict time frames and on tight budgets — a challenge familiar to anyone who has a working background in QA.

On a related note, a QA background can instill a CEO with an enhanced ability to manage expectations regarding hitting a company's clinical and regulatory milestones. QA is a science, after all, and doing science — as working researchers can attest — is sometimes hard and unpredictable. In providing periodic reports of the company's progress to the street, it is vital for the CEO not to overpromise. Having firsthand QA experience, complete with knowledge of the challenges and setbacks this endeavor can entail, provides a sense of what is possible within a given time frame. Thus, there is less of a temptation to exaggerate how much can be accomplished in the next quarter.

## PATIENT ADVOCACY

Having also had previous experience with patient advocacy, the value of this activity to a CEO's background is clear to me, as well. Working with the heads of various advocacy groups (in my case, those focusing on a rare skin disorder) involves being introduced to patients and also becoming familiar with their expectations (as well as those of their families) about potential treatments. A CEO of a small biotech can likely personally meet with these groups on a regular basis rather than rely on a separate director of advocacy initiatives.

> *"A QA background can instill a CEO with an enhanced ability to manage expectations regarding hitting a company's clinical and regulatory milestones."*

Patient advocacy experience also is a feather in the cap of someone who moves into the role of a biotech CEO

## BACKGROUND/DEGREE/EXPERIENCE OF SOME OF THE TOP BIOPHARMA LEADERS

| NAME | COMPANY | EXPERIENCE |
|---|---|---|
| Ian Read | Pfizer | chemical engineering & accounting |
| Joseph Jimenez | Novartis* | economics |
| Severin Schwan | Roche | J.D. law |
| Kenneth Frazier | Merck | J.D. law |
| Olivier Brandicourt | Sanofi | A physician by training, holds advanced degree in cellular and immunological pathophysiology and a master's degree in biology |
| Alex Gorsky | J&J | bachelor of science degree, MBA |
| John Milligan | Gilead | Ph.D., biochemistry |
| Emma Walmsley | GSK | master's degree in classics and modern languages |
| Richard Gonzalez | AbbVie | No degree, was a research biochemist at the University of Miami School of Medicine |
| Robert Bradway | Amgen | bachelor's degree in biology, MBA |

*New Novartis CEO, Vasant Narasimhan, is an MD.

because it means these groups know they have a friend at the very top of the organization who understands their needs. Some CEOs without this experience might appear less approachable to the heads of advocacy groups. In contrast, when an advocacy group has established a clear line of communication to CEOs — being able to email and call them, for example — there is an additional bond between the company and these external groups that helps each work in tandem more efficiently. A patient advocate CEO is a valuable humanizing factor.

### INVESTOR RELATIONS

Another rung in my personal ladder to CEO was serving as head of operations at my company, which in turn, served as a conduit that exposed me to the investment community. For any biotech CEO, having previous experience interacting with investors is a tremendous advantage. This experience can come in the form of attending bank/investor meetings, industry talks, non-deal and deal road shows, as well as being involved in financial raises for the company. And because the investment community is becoming so well-educated these days — even going so far as to recruit their own M.D.s/Ph.D.s to ask questions — it is always a plus for the CEO to have some scientific background, as well, when dealing with investors.

Being able to view milestones and other expectations from the perspective of investors can give a CEO a leg up when dealing with them. When you are helping to raise money for your company, you really get a taste of how the financial culture works. When someone with this type of experience reaches the CEO's chair, it can help them focus on how activities are conducted internally, keep clinical trials moving efficiently, and maintain a level of discipline that maximizes hitting milestones in a timely fashion. A CEO without extensive investor relations experience should not shy away from enlisting the help of financial professionals to bolster this task.

### TEAM BUILDING

Finally, any CEO who has risen through a biotech company's ranks is bound to develop a stronger sense of what makes the entire company — viewed as a set of teams working in tandem — operate well. Particularly with smaller biotechs, which run relatively lean compared to larger companies and have fewer levels of management between workers and C-suite, it is beneficial for the CEO to interact directly with the entire staff on a regular basis. Having experience leading individual teams, such as those working on research and clinical study design, can create a more practical management style for a CEO.

Having that experience also means it will be easier to manage teams tasked with achieving goals related to manufacturing and production. There is a converse benefit as well: Current members of these teams, being aware that the CEO was once part of the rank and file, may be more willing to appreciate their efforts to facilitate their tasks. This "been there, done that" factor works wonders for the CEO when meeting one-on-one with workers as they discuss their concerns and seek advice in turn. Overall, this lends itself to a greater sense of camaraderie and sense of purpose.

CEOs who are able to leverage their background experience in various areas, as discussed here, are in a good position to move their company forward. The wider the experience they can draw on, the stronger they and their business ultimately become.

JOHN MASLOWSKI is president and CEO of Fibrocell Science, Inc., a gene therapy company focused on transformational autologous cell-based therapies for skin and connective tissue diseases.

# Madrigal Pharmaceuticals

Taking on NASH and other liver diseases by targeting the thyroid hormone beta receptor

**WAYNE KOBERSTEIN** Executive Editor
@WayneKoberstein

## SNAPSHOT

Madrigal is developing a thyroid hormone beta (THR-β) analog, coded MGL-3196, a selective THR-β agonist for treating multiple conditions. MGL-3196 is in late Phase 2 studies in NASH (nonalcoholic steatohepatitis) and heterozygous familial hypercholesterolemia (HeFH). Madrigal also has a follow-up THR-β agonist, MGL-3745, in preclinical development for NASH and HeFH.

## WHAT'S AT STAKE

Liver damage is an old concept few people probably seek to understand further. But what does the damage actually entail? How and where in the liver does it occur? According to the current science, morbid liver conditions such as NASH cause damage right down to the intracellular level, crippling the organelles and the cytoskeleton of individual liver cells. Madrigal came into being based on understanding how the cellular damage might occur, with a key component being insufficient activity of thyroid hormone specifically in the liver.

Thyroid hormone is essential to normal liver function, and the livers of NASH patients are typically hypothyroid, but THR has multiple effects on the liver through two types of receptors, alpha and beta, each with a specific set of functions. Why then target only THR-β, not also THR-α? In short, it is because agonizing the beta form addresses the key features of NASH without causing side effects such as increased heart rate or osteoporosis, as targeting the alpha form does. A THR-β agonist treats the metabolic syndrome associated with fatty degeneration, lipotoxicity, inflammation, "ballooning" and apoptosis of liver cells, and fibrosis in NASH. As a bonus, the Madrigal drugs appear to lower LDL cholesterol and other lipids such as triglycerides overproduced by the liver in the course of the disease.

The foundational R&D for the company's drug candidates began about 15 years ago in the metabolic research group at Roche in Nutley, NJ, under the leadership of Madrigal's founder, Rebecca Taub, M.D. Taub was already an industry veteran at that point but one with an entrepreneurial bent. When she left Roche in 2008, she managed to license the program from Roche and started searching for a way to continue it in a small company. "I was very interested in these THR-β agonists for NASH therapy long before the NASH area exploded in the past few years," she says. First, Taub transferred the license to a small public company, VIA. A few years later, VIA spun off Madrigal, along with Taub's metabolics program. Now chief medical officer and head of R&D, Taub served as Madrigal's CEO until Paul Friedman, M.D., joined the company in 2016 as chairman and CEO. Friedman is also a long-time industry executive.

Friedman took over as CEO following Madrigal's reverse merger with a subsidiary of Synta, which took the company public and generated funds to move the metabolics program forward. "Becky and I put money into a private placement before the reverse merger closed to pick up the pace in the drug development and get the two studies started," Friedman says. Taub explains that her group at Roche used a novel assay to assess the function of its test molecule at the THR-β receptor: "It wasn't a simple binding assay. It looked at the ability of the compound to interact with the receptor and regulate the THR-β hormone in the liver. From bench experiments to animal studies to human studies, we've shown our molecule is unique in its THR-β receptor activity," she says.

"Our molecules are highly protein-bound and have a polarity that prevents them from diffusing into cells and from crossing the blood brain barrier," adds Friedman. "They are taken up selectively by transport proteins in hepatocytes, which is highly useful from both safety and targeting standpoints."

This is a good time to watch this company. Madrigal expects to begin seeing top line Phase 2 trial results on MGL-3196 in late 2017, with more released in 2018.

**PAUL FRIEDMAN, M.D.**
Chairman & CEO

**REBECCA TAUB, M.D.**
Chief Medical Officer & Head of R&D

### Vital Statistics

**9**
Employees

**Headquarters**
Conshohocken, PA

### Finances

**Public**
Via the founding merger in 2016

**Raised**
**$45M**
via additional equity financing

**Largest Investors:**
Bay City Capital, Baker Brothers, SQN LLC, Adage Capital Management, Rock Springs Capital Management, Armistice Capital

### Latest Updates

**June 2017:**
$35M equity financing

**August 2017:**
Completion of enrollment in Phase 2 proof-of-concept study with MGL-3196 for treatment of NASH

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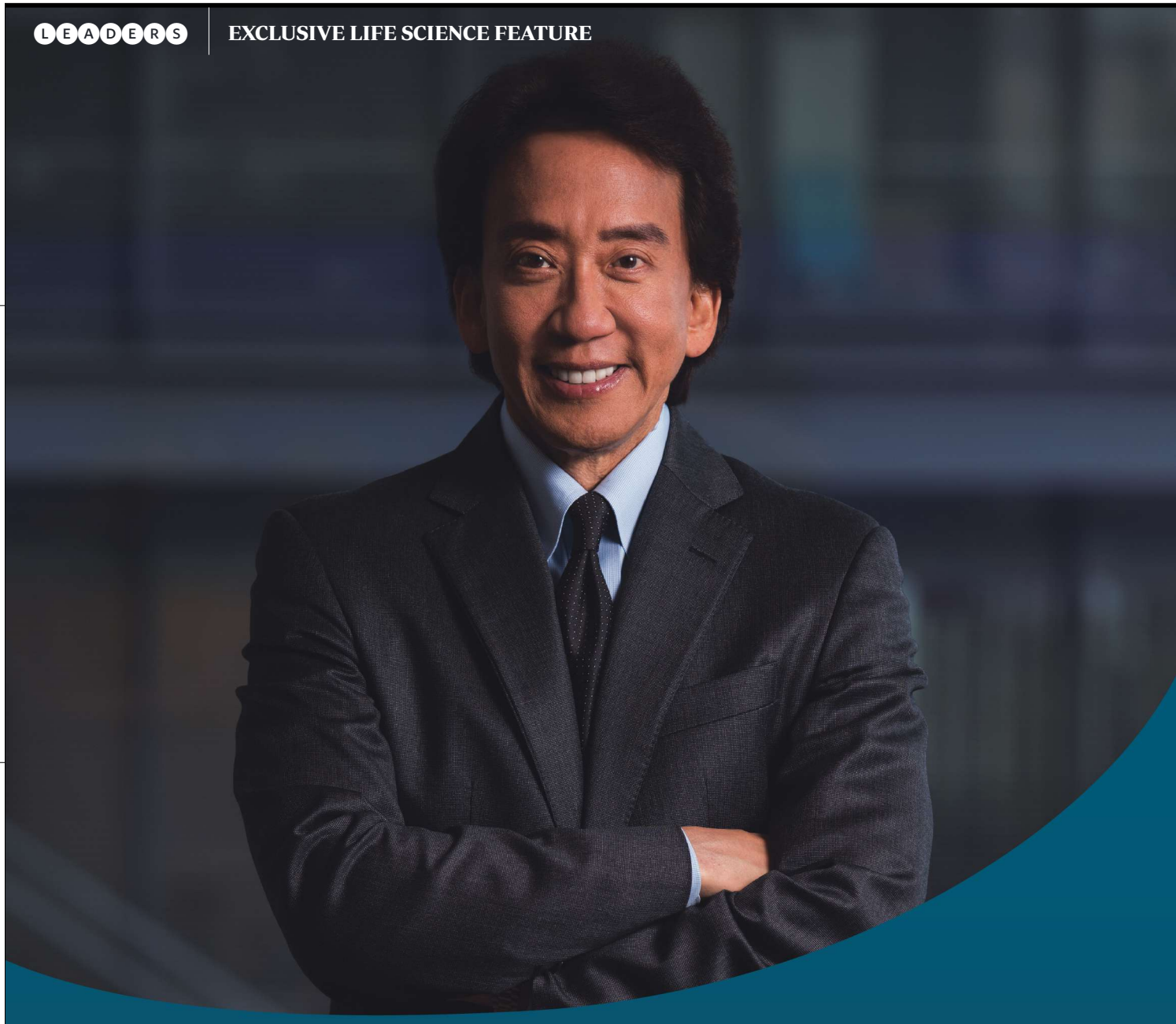

# Can David Hung Lead Axovant To **Alzheimer's Success?**

**ROB WRIGHT** Chief Editor @RfwrightLSL

# "I couldn't get a job in biotech," says David Hung, M.D.

Having completed medical school, a residency, two basic science research fellowships, and three clinical fellowships, Hung had spent his entire career in academia. So why was he even looking to leave? "I was in the third year of a fellowship when a patient of mine, a 28-year-old woman, died of metastatic breast cancer," he explains. "This had a profound impact on me, and I decided right then and there I wasn't going to spend the rest of my life practicing as a clinical oncologist armed with only the currently available technologies that couldn't prevent the death of someone so young."

But Hung had a problem. Despite being highly trained, because he lacked previous biopharmaceutical industry experience, no one seemed willing to give him an opportunity. "I applied to 35 biotech companies before someone finally took a chance on me." That company was Chiron, an American multinational biotechnology firm based in Emeryville, CA. Then, just when he was getting his start, Hung encountered an additional piece of adversity. "It was 1996, and I was in my first week at Chiron when I got appendicitis and couldn't go to work." Being laid up, his boss suggested he put some thought into preparing for an upcoming Chiron scientific retreat, and the rest is, as they say, history.

He would go on to start Medivation, a company he eventually sold to Pfizer for $14.3 billion. But his career path, and its inherent challenges, wouldn't stop there. In April of this year, he became CEO of Axovant Sciences, a clinical-stage biopharmaceutical company focused on treatments for dementia and related neurological disorders. Among those disorders is Alzheimer's disease, a therapeutic area synonymous with drug failure. In fact, Hung had experienced failure in this area before. So why, this late in his career, would he join such a company? And why would he agree to invest $10 million of his own money into the business?

Those are exactly the kinds of questions I asked him when we sat down to talk at the 2017 BIO International Convention in San Diego. But first, we started at the beginning.

## WADING IN AT CHIRON

When Hung was recuperating from appendicitis during his first week at Chiron, he had a big idea. He had been assigned to work on a tissue factor pathway inhibitor (TFPI), an anticoagulant Chiron was developing for sepsis. While on this project, he pondered why hemophiliacs bleed. That line of thinking eventually led him to raise the following question at the Chiron retreat: Instead of treating hemophilia with recombinant factor 8, or fresh frozen plasma (which has infectious risk), what if Chiron attempted to develop a small molecule treatment for hemophilia by inhibiting the inhibitor (i.e., TFPI)?

Bill Rutter, Ph.D., the founder of Chiron, happened to be in the audience and, afterward, asked Hung to come to his office. Rutter asked Hung what he would do if he were running Chiron. "I told him I would run it as a smaller, virtual organization and proposed setting up a side, virtual drug development organization with a goal of developing compounds faster, cheaper, and better than I believed could be done within Chiron." Rutter, along with Lewis T. "Rusty" Williams, M.D., Ph.D., who was then the head of Chiron Technologies, decided to give Hung his shot, tapping him as the head of new projects and setting him up to operate virtually. "This was probably a little presumptuous, given the fact that I had no previous industry experience, but they believed in me, and I was given the freedom to pretty much do whatever I wanted," he grins. "Every one of the programs we started in the new projects division hit their milestones, and a number went on to show significant signals in the clinic." According to Hung, every year Chiron conducted a net present value (NPV) analysis of the programs in development. Three years after he started, more than 50 percent of the NPV of Chiron's therapeutic programs came from the new projects division. Hung eventually proposed that Chiron spin him off as his own company, along with some seed capital. "I was all set to go, but then the company had a change in senior management." The new CEO didn't want to spin off the division, so Hung ended up leaving.

## A STINT IN THE WORLD OF MEDICAL DEVICES

Hung's next stop was at medical device company Windy Hill Technologies (later named Pro-Duct Health), which focused on early detection and diagnosis of breast cancer. "Considering a young patient dying from breast cancer is what prompted me to leave academia for industry, it almost seemed prophetic to return to this therapeutic area," he states. Still, just as he had no previous experience in biopharma prior to Chiron, here he was again facing a new industry — medical devices. When asked about such a leap, he explains a philosophy he's adhered to throughout his career. "When I think about how to

create the best options for patients, I'm not wedded to any particular therapeutic approach or medical discipline," he explains. "I just look at what it takes to develop something from which patients will really benefit."

One of the most widely used early breast cancer detection tools is a mammogram, which can detect a tumor about one centimeter in diameter. According to Hung, the process of a tumor going from one cell to about a billion cells (the approximate number of cells it takes to make up a one centimeter-sized tumor) takes about 10 years. In other words, early detection by mammography is actually not very early. So Hung set out to come up with an earlier-detection tool.

"When a woman nurses a baby, the little holes in her nipple that milk comes out lead to a series of tubes," he explains. "One hundred percent of all ductal breast cancers begin in the cell layer that lines those tubes." Hung invented a microcatheter (about the thickness of three human hairs) that could be put into the nipple through the same holes that milk comes out of. Cells are washed out of the milk ducts (i.e., ductal lavage), and a slide is prepared and analyzed in a manner similar to a pap smear. In a clinical trial of 507 high-risk women, Hung and colleagues demonstrated that not only could they identify cancerous cells that could not be seen on a mammogram, but they could successfully identify precancerous cells. "We got very lucky, because the landmark breast cancer study, NSABP P1 [The National Surgical Adjuvant Breast and Bowel Project, Prevention-1], came out within a few years of our ductal-device study," he says. "If you could identify precancerous lesions in women considered high risk for breast cancer, defined as women having a GAIL index of 1.7 percent or higher, and give them Tamoxifen, their chance of getting breast cancer was reduced by 86 percent." At the time, Pro-Duct Heath had the only FDA-approved noninvasive way of finding those precancerous lesions in the breast, and in 2001, the company was acquired by Cytyc Corporation (today known as Hologic) for $167.5 million. "That was my first experience with an acquisition," Hung shares. It wouldn't be his last.

## SURVIVING A HARD LESSON LEARNED

Following the acquisition of Pro-Duct, Hung took a year off to think about what he wanted to do next. "Even though I'm an oncologist, I decided Alzheimer's disease was the most important affliction facing patients in society," he shares. "The total cost of Alzheimer's-related healthcare is more than double all of cancer, and by 2050 there are going to be more than 100 million people with Alzheimer's disease." In preparing to tackle Alzheimer's, Hung spent the next two years reading as much as he could on the basic science and clinical literature of the disease. "The last thing I wanted to do was develop a company that would develop me-too drugs," he explains. "So, I started Medivation in 2003, which was named because I wanted to focus on products that represented true medi-cal inno-vation, because the world doesn't need more drugs, it needs better drugs."

Based on his literature review, Hung concluded that Alzheimer's and neurodegeneration might best be addressed with drugs targeting various aspects of mitochondrial pathology in neurons. "I looked at about 300 different technologies worldwide and stumbled across this drug from the Russian National Academy of Science [RNAS], Dimebon [pronounced dim-eh-bon]," he says. "I was intrigued by the molecule because the Russians had been testing it in rodents, and those that had been given Dimebon shortly after birth exhibited far less signs of aging when compared to the rodent control group of similar age [i.e., fewer cataracts, less balding, less greying, and less cachexia]." Seeing the Russian results, Hung theorized that perhaps Dimebon affected mitochondria and thus, in-licensed Dimebon to be Medivation's first drug. "It had already been approved in Russia for use as an antihistamine, so we initially spent a lot of time characterizing its effects in neurons and put the drug into several clinical trials for Alzheimer's patients."

One of the first trials the company conducted was a six-month randomized, double-blinded, placebo-controlled Phase 2 clinical study of 183 patients with mild to moderate Alzheimer's disease at 11 sites in Russia. It remains one of the most robustly positive trials ever conducted in Alzheimer's. "Dimebon-treated patients showed statistically significant improvement over baseline on all five efficacy endpoints in this study ($p < 0.05$), so we were highly encouraged," Hung shares. "The results were compelling enough that the FDA said they would accept this Phase 2 trial as the first of two pivotal studies for Alzheimer's, and if we hit a second trial, we would get approval." Unfortunately, the company was not able to reproduce the same results in its Phase 3 study. "We were crushed, as were all of our patients and families when the trial failed," Hung admits. "We were reviled by the press, our investors weren't happy, and in the first hour of trading after the announced failure we lost more than $1 billion in market cap." And though Medivation ended up laying off about one quarter of the company, there was a silver lining. "The experience taught us a lot about what it means to fail as a team and the importance of continuing to work and remain galvanized toward a common mission," he states. That perseverance was put to the test about a year and a half later when another product in Medivation's pipeline, Xtandi (enzalutamide) for late-stage castration-resistant prostate cancer, received very positive results.

Xtandi went on to gain FDA approval in 2012, and

Medivation eventually ended up being acquired by Pfizer in 2016 for $14.3 billion — one of the largest all-cash deals in biopharma history involving a founding CEO. Though Hung walked away from the deal with around $350 million, he decided not walk away from biopharma — or his desire to tackle Alzheimer's disease.

## ALZHEIMER'S DRUG DEVELOPMENT — AN ITCH IN NEED OF SCRATCHING

Last summer while Hung was at the 2016 U.S. Open men's tennis final, he ran into Vivek Ramaswamy, the founder of Roivant Sciences (i.e., Axovant Sciences' parent company). (See "What's The Backbone Of Vivek Ramaswamy's Success?" in our April issue.) The two men had known each other for at least 10 years, as Ramaswamy had been a junior analyst at QVT, one of Medivation's biggest shareholders. Soon thereafter, Ramaswamy asked Hung to come run Axovant. "I had been so swamped with executing the Medivation acquisition that I really didn't know a whole lot about the company," Hung explains. But as he began to take a deeper look, he became intrigued. Remember, when he founded Medivation, its original goal was to develop a treatment for Alzheimer's disease. Although he had success with Xtandi, his failure with Dimebon created an Alzheimer's drug-development itch that had remained unscratched. "As I did my due diligence, I saw an interesting opportunity to try to get approval for a new Alzheimer's drug," he shares. "So I decided to sign on."

Pursuit of a successful Alzheimer's therapy is not for the faint of heart. Thus far, drug candidates for the disease have a 99.6 percent failure rate, and poor early-detection methods make clinical trials costly and difficult. Hung did not let such dismal statistics and previous failures discourage him from taking on the Axovant opportunity. In fact, when he signed on to become Axovant's CEO, he even invested $10 million of his own money in the company (see sidebar — "Hung's Philosophy When It Comes To Investors"). So why such enthusiasm for a company he barely knew? He says one of the key factors was Axovant's lead candidate, Intepirdine, a cast-off compound (SB742457) 5-HT6 receptor antagonist acquired by Ramaswamy from GSK for a mere $5 million.

"Recent and notable Alzheimer's drug-development failures, such as Lilly's Solanezumab and Pfizer and Janssen's partnership to develop Bapineuzumab, were therapeutic approaches targeting the same target, beta amyloid protein. I don't put all Alzheimer's therapeutic strategies in the same category of risk. If you look at the four drugs approved today for Alzheimer's disease, three — Aricept (donepezil), Exelon (rivastigmine), and Razadyne (galantamine hydrobromide) — target cholinesterase, the enzyme that degrades acetylcholine." Acetylcholine is an extremely well-validated target with 30 years of research and the approval of four agents. A fourth cholinesterase inhibitor, tacrine, the first drug approved by the FDA (1993) for Alzheimer's disease, was taken off the market because of adverse events. "When you inhibit cholinesterase, you may reduce the degradation of acetylcholine, but it doesn't put more acetylcholine in your synapse," Hung explains. Axovant's Intepirdine is an antagonist of the 5-HT6 serotonin receptor, a largely CNS-specific member of the serotonin receptor subfamily. "When you inhibit that receptor, you actually put more acetylcholine in your synapse." Hung analogizes how Intepirdine works in treating Alzheimer's as "putting more juice in your cup as opposed to making a leak in the cup smaller [which is what cholinesterase inhibitors do]." And while the Intepirdine Phase 2 data is strong, Hung is hopeful that the compound's Phase 3 "MINDSET" trial (a 24-week, international, multicenter, double-blind, placebo-controlled clinical study, involving 1,315 patients with mild-to-moderate Alzheimer's disease) will not only validate his belief, but result in the first new Alzheimer's drug approved in 15 years. "I'm not saying this is not a high risk, as Alzheimer's disease is extremely complex and multifactorial," he concludes. "But some risks are worth taking."

## HUNG'S PHILOSOPHY WHEN IT COMES TO INVESTORS

David Hung ran Medivation for 13 years. When the company was acquired by Pfizer, he still owned more than 90 percent of the stock options ever granted. Some might wonder why? "I really believed in what I was doing and firmly believe in always putting my investors first, so they benefitted before I did," says the company's former CEO. Case in point: Dr. Hung founded Medivation in October 2003. During the life of the company he raised a total of only $440 million in public offerings. So when the company reached a market cap of more than $14 billion, Hung effectively provided Medivation investors with an ROI of nearly 21,000 percent! (That is not a typo.)

Hung is applying a similar approach in his new role as the CEO at Axovant. As if to punctuate his point, he jams his index finger onto the table making an audible thump, and says, "I put my own money – $10 million – in on the same terms as the last financing, as I want to make sure that I set the bar high enough for my own option-investing schedule. I want to create real value for my investors before I get rewarded."

In deciding to sign on as Axovant Sciences' CEO this past April, Hung had significant input into the structure of his compensation package, which is anything but a golden parachute. For example, the executive will get 6 million Axovant options in total. Two million options are tied to the stock price (NYSE: AXON) on December 29 of this year. Further, most of those options only vest if the stock increases by 1.5 times from December 29. Another 2 million options carry an exercise price of $15.13, most of which only vest if the stock hits $100 (nearly a $78/share increase from where it is presently trading) and the company's lead Alzheimer's candidate (Intepirdine) trial is successful, or $15 if the trial is a bust. The remaining 2 million options are tied to Axovant's stock price prior to the announcement of Hung being named CEO (i.e., exercise price of $15.13). In other words, for Hung to reap significant financial rewards at Axovant, he must first deliver significant financial rewards to his investors.


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**JEFFREY BERKOWITZ**
*Formerly of UnitedHealth Group/Optum*

**JEREMY LEVIN**
*Ovid Therapeutics*

**DAVID MEEKER**
*Formerly of Sanofi Genzyme*

"As the price of pharmaceuticals continues to rise, we are seeing greater resistance from [U.S.] patients being willing to pay," says Dr. Steven Miller. The SVP and chief medical officer at Express Scripts is giving his opening remarks during the Our Common Goal: Ensuring Access and Affordability of Innovative Medicines session at the 2017 BIO International Convention in San Diego. Miller pulls no punches with his fellow biopharmaceutical executive panelists, setting the tone that today's discussion on drug pricing will not be a "hugfest."

Billed as a one of the "can't miss educational sessions for BIO 2017," panelists included an insurance industry executive (Steven Miller, M.D.), two biopharmaceutical industry executives (Jeremy Levin, D.Phil, MB BChir, CEO of Ovid Therapeutics and David Meeker, M.D., former EVP of Sanofi Genzyme) and one executive who spanned biopharma, retail pharmacy, drug distribution, and insurance (Jeffrey Berkowitz, formerly EVP at Merck, Walgreens Boots Alliance, and UnitedHealth Group). Actually there were three biopharma execs if you include the moderator, Ron Cohen, M.D., CEO of Acorda Therapeutics. As three of the five participated in a special drug pricing roundtable published in *Life Science Leader's* July 2016 issue, it seemed like a great opportunity to provide an update on this seemingly ever-controversial topic — which we will do in two parts.

# Can We Make Innovative Medicines Affordable?

## An Insightful Discussion On Drug Pricing – Part 1

**ROB WRIGHT** Chief Editor @RfwrightLSL

**COHEN:** In the U.S., we struggle to achieve a balance between allowing biopharma to continue to accelerate as an innovation machine, while at the same time, figuring out how the system can best pay for these goods and services, which are often more costly when compared to the rest of the world. Each panelist will now provide an introductory statement.

**MILLER:** America represents 4.6 percent of the world's population, yet takes about 33 percent of drugs by dollar volume and represents between 50 and 70 percent of the pharmaceutical industry's profitability. For a long time, the U.S. has been funding medical innovation for the world. But as the price of pharmaceuticals continues to rise, we are seeing greater resistance from patients being willing to pay. This resistance is driven, in part, by the U.S. having higher-priced drugs as compared to the rest of the world, and more people being subjected to incredible out-of-pocket payments. For the most part, high-deductible health plans are designed for rich people, yet are most often sold to poor people. And when a poor patient with such a plan goes to pick up their medication and learns they will have a high out-of-pocket payment, they often end up leaving it at the pharmacy. So all the great things the biopharma industry is inventing aren't getting to those who need them.

**BERKOWITZ:** The drug pricing problem isn't going to be solved by biopharma continuing to work on extremely important science without engaging other key healthcare ecosystem stakeholders. Though there has been a significant consolidation, we continue to reside in a world where many healthcare industry stakeholders are talking at each other. Biopharma needs to do a better job engaging with the rest of the healthcare ecosystem regarding what they are working on, and the rest of the healthcare ecosystem (i.e., insurance payers, providers, PBMs, and retail pharmacies) need to improve their level of engagement with one another. Finally, there needs to be accountability at the highest levels of biopharma organizations to better understand where and if their products fit commercially in a consolidating marketplace.

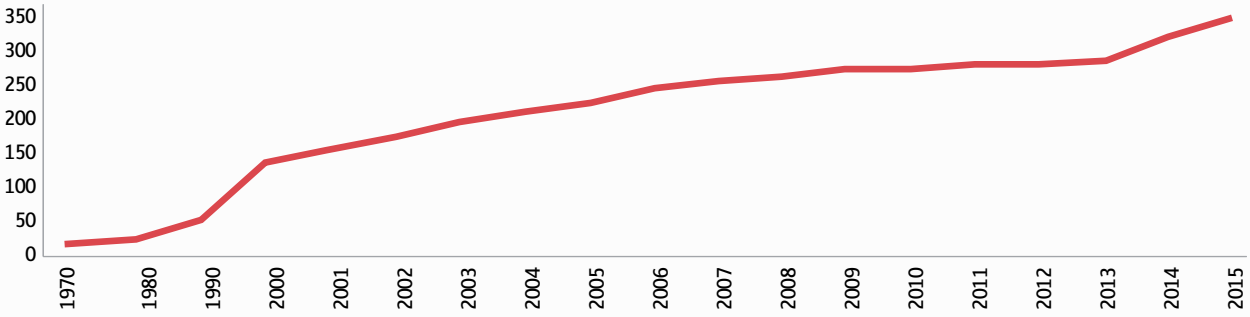
**LEVIN:** As the CEO of a biopharma company, it is my job to see what I can do to improve our healthcare ecosystem. I do not believe presidential orders, congressional oversight, or massive policy changes are at the core of what is necessary to correct the current drug pricing issue. However, I do believe certain aspects of our healthcare system and industry can be changed to impact pricing and unacceptable patterns of price rises, and to do that all healthcare industry leaders need to step forward, a process which begins with how they approach leading their own organizations.

**MEEKER:** The challenge isn't the process of innovation, but how to get these innovations to the individual patient (i.e., access and affordability) most efficiently. If we work backwards from that, we will find the necessary savings in our relatively inefficient healthcare system to allow that to happen. But you can't have one stakeholder working individually toward solving the problem. Viable solutions require a holistic and collective approach involving all stakeholders being willing to give on their own points of inefficiency.

**COHEN:** In addition to patients not being able to afford their co-pays or coinsurance, sometimes they can't get their prescription because the insurance company or PBM imposes certain step edits or prior authorizations on the physician to prescribe a given medication. To this we can add PBMs blaming drug companies for high drug prices, and drug companies highlighting PBMs accepting big rebates that don't specifically help the patient afford their prescription. So how do we address this situation?

**MILLER:** Manufacturers use rebates to either reward or punish. For example, if a PBM puts a drug on its formulary, manufacturers give the PBM a discount via a rebate. If a PBM doesn't put the manufacturer's drug on its formulary but instead puts a competitor's drug on its formulary, they punish the PBM by charging it more, giving less or no rebate at all. PBMs benefit from getting higher rebates because they take a percent of that rebate, which helps achieve the goal of selling drugs at the lowest net cost. The U.S. drug rebate system, with all of its pros and cons, is a legislated legal requirement by government for Medicare and, as such, won't be going away anytime soon. That being said, PBMs are working to make drug pricing more transparent for patients. For example, Express Scripts developed a program called InsideRx to offer lower rates for select groups of frequently used drugs. The program was designed for patients without insurance or those with high-deductible insurance plans, as these people were the only ones paying list price. Consumers can sign up for free and, if they qualify, use a discount card or mobile app to get a rebate at the point of sale. Essentially, we are jury-rigging a maladaptive system.

## MONEY SPENT ON PRESCRIPTION DRUGS (IN BILLIONS)




DATA FROM THE FDA AND CMS

**BERKOWITZ:** Jury-rigging is a good way to put it, because we still operate in a traditional system that hasn't changed. I find it remarkable that members of the healthcare ecosystem put very little thought into figuring out how to best get a new drug into a patient's hand. It isn't until maybe three to six months prior to a new drug's launch/approval that biopharmas begin meeting with PBMs. Yet, for PBMs to understand the science and the problem a biopharma's innovation is trying to solve, engagement needs to begin earlier. There has been so much consolidation and integration that there are only a few conversations needed between a biopharma company and other industry stakeholders. Today in the U.S., there are about five national health plans, two retail pharmacy chains, three PBMs, and three specialty pharmacies that really matter. Biopharma having conversations with these stakeholders at the earliest stages should provide enough information to help make more informed drug pricing and reimbursement decisions.

**LEVIN:** It is interesting to hear the description from Jeff of the small handful of players with which biopharma companies need to engage. However, one cannot underestimate the impact that both the lack of training or the access to employees in biopharma companies who understand or can initiate the necessary dialogue on the biopharma side for this "earlier engagement." For large companies that might have many people working on access with key healthcare industry stakeholders, this dialogue is relatively straightforward. But the majority of small biopharma companies where innovation is the primary focus of investment simply don't have the resources necessary to have those meaningful discussions, let alone know who to go to talk with or often why it's important to engage early. Generic companies understand access well as they deal with huge volumes and multiple drugs. These companies meet routinely with payors, pharmacy chains, and PBMs, often at selected venues and conferences. For large branded biopharma companies, the system of access is focused on individual innovative products.

**MEEKER:** You mentioned the jury-rigging part of this. Is that the only way forward? Are we resigned to only being able to make small, incremental steps to address the drug-pricing patient-access problem?

**MILLER:** We are at an inflection point as we move away from a pricing model built on volume and toward one built on value. Value-based contracting has actually required people from biopharma and insurance to start engaging, because it's not just a transaction (i.e., put my drug on formulary, and I'll give you a rebate). For example, when Regeneron and Sanofi were bringing dupilumab (a new treatment for adults with uncontrolled moderate-to-severe eczema) to market, they went on a listening tour with everyone Jeffrey Berkowitz just described. The companies wanted to have a deep understanding of reimbursement and understand our pain points. This helped Express Scripts better understand their pain points, as well as how the drug was going to work. If you look at the results, Regeneron and Sanofi brought dupilumab out at an incredibly reasonable price (i.e., $37,000). While not cheap, when compared to another psoriasis treatment costing $65,000, it's nearly half-price. The companies even received a positive response from a review by the Institute for Clinical and Economic Review (ICER). Express Scripts has since had similar positive experiences with Genentech's new MS product, OCREVUS (ocrelizumab), and Radius Health's osteoporosis drug, TYMLOS (abaloparatide). What I just described is what the future needs if we hope to create a sustainable business model.

**LEVIN:** There will be a moment where for all medicines an understanding of what is a meaningful medical impact will have to be established in order to incorporate value into the pricing model. For example, one of the disorders my company works on is Angelman syndrome. A mother of a child with Angelman syndrome will tell you that a "meaningful difference" in their child is their having the ability to better communicate. Most children with Angelman syndrome suffer from

a number of disabling conditions including cognitive problems, epilepsy, and insomnia, and many don't easily communicate verbally. Some have learned to use a few signs of American Sign Language (ASL). For the parent of a child who uses just one sign, learning two will be a tremendous benefit. In those families, the same sign is used to tell the caregiver or parent they need water, want to sleep, etc. But if the child could, following treatment with a medicine, suddenly have two signs, suddenly these children are able to communicate much more clearly. So the concept of meaningful impact and therefore value of a drug will need to be better understood by the payor, the regulators, and the system taking care of the patients and, in doing so, incorporated into the pricing model.

**MILLER:** Such education has to start much earlier and requires repetition. Biopharmas need to be meeting with other healthcare ecosystem stakeholders two years before the product is in the pipeline, and you will need to come back throughout the process. Only over time will we together figure out if a payer is actually going to reimburse for that "meaningful" difference.

**COHEN:** Let me go back to the question: "Are drugs too expensive?" But for this discussion, let's leave aside drug price increases for products that are already on the market.

**MEEKER:** The classic statistic of drugs representing only 14 percent of the total healthcare spend has been relatively stable over time and, as a percentage, does not differ greatly around the globe. The issue isn't whether we are spending too much on drugs in the aggregate, because that 14 percent figure includes 90 percent of prescriptions filled by generics. The question is: Are drugs too expensive for any given individual? I would love a system where I can get a fair price for those people who can afford to pay for it, and for those who can't or fall outside of the system, I would be happy to give the drug away for free.

**BERKOWITZ:** But with that approach, you are still jury-rigging the system (i.e., robbing from Peter to pay Paul). It's not so much that drugs across the board are expensive, but are you looking at a particular therapeutic class, and a particular need of a particular product, at a particular point in time as a drug is launched. Dupilumab is an example of a product brought to a market that was understood with regard to expenses and pain points. The company had a solution that provided a different outcome of value for the system and the patient and believed they would be reimbursed if it was priced a certain way.

**COHEN:** I'm going to posit that if Regeneron and Sanofi came out with a $37,000 price tag for this drug back in 1980, everyone would have completely lost their marbles.

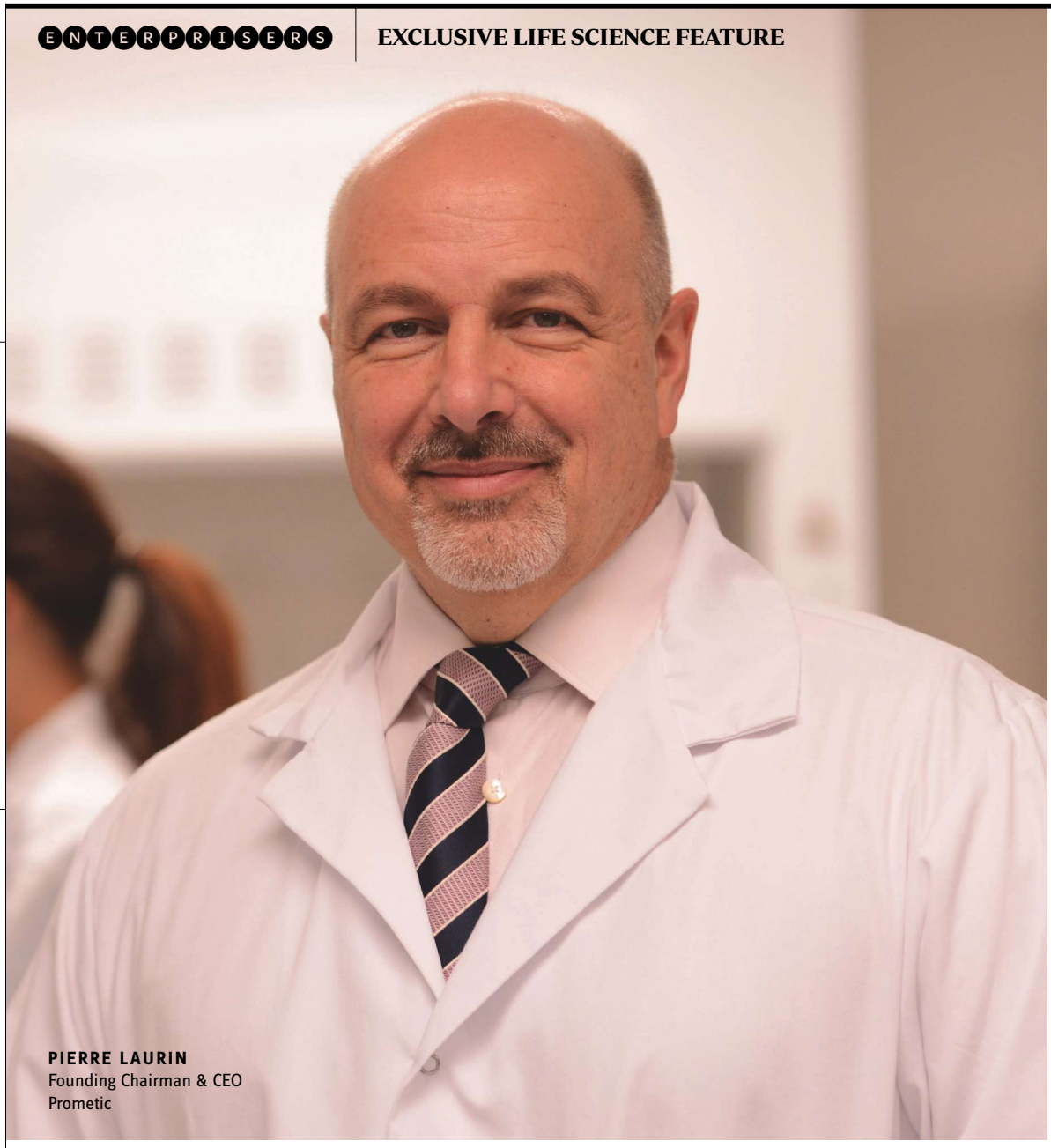
**MILLER:** That happened when Genzyme developed an enzyme replacement therapy that was priced at $300,000. However, the company never raised the price. A stable drug price that doesn't increase from when it was launched is what actually happens in almost every other country. When drug companies launch a new drug and announce what the launch price is, they theoretically calculated in what was needed from a return on investment perspective. Only in America do we see cases where drugs are launched at one price, and then price increases are taken over the years. For example, Gleevec was launched at $30,000 a year, yet it went up to over $100,000. Viagra came out at $7 a tablet, and yet it went up to around $50. These are two drugs with zero rebates, so the price increases can't be blamed on anyone but the manufacturer. If you ask the average American consumer, "Are drugs too expensive?" Yes. Does the pharma industry deserve a percent of GDP forever? Absolutely not. This idea that biopharma is and always will be only 14 percent of healthcare costs is a fallacy. Every aspect of healthcare in America is more expensive than it is in the rest of the world, and our results are not as good as other Western countries.

**LEVIN:** I helped launched Ceredase, the $300,000 drug and, like all involved, take great pride in the fact that Henri Termeer never increased the price, and yet the drug was accessed by a tremendous number of those Gauchers patients who needed it. This shows us that it's not the just the initial price that is central to the issue, but rather the subsequent price increases that are the problem. Many of these rises are unconscionable because there is no change in the effect of the drug and often no label expansion or investment to show additional benefits. This is something that the industry can actually do something about. The insulin patent was sold to the University of Toronto by Banting, Best, and Collip for three Canadian dollars in 1921 with the explicit hope that diabetics could have affordable insulin forever. This has not been the case, and prices have risen consistently and sometimes very significantly even for the older, unpatented forms of insulin. How do we address this? For starters, companies can take a stand by not rewarding executives through cancelling

incentive compensation for price increases. Every biopharma compensation committee on every corporate board can review how their CEO and senior management are compensated and can create systems that incent innovation and not incentivize or even, where possible, disincentivize, price increases. Companies focused on price rises tend not to focus on innovation. But it is innovation that drives a sustainable industry.

**MEEKER:** Unfortunately, the Shkreli example, which is an outlier, has become the poster child for the drug-price-increase problem. The bigger issue is the 10 to 20 percent price increases that get taken on a yearly basis to meet earnings. These are what are going to break the system. My biggest concern is that absent industry self-regulation, we will be regulated, and if we are regulated, the market forces and the incentives that have allowed the U.S. biopharma system to exist will end, as will the innovative R&D. Industry needs to step in and be a part of fixing this, and our efforts need to be more visible. At Sanofi we made a statement that we were not going to take price increases greater than the national health expenditure, which was 5 percent last year. That statement came out of internal drug-price increase dialogue that began six years ago. As an industry, I hope we can give such self-managed initiatives a chance to work. When we brought Kevzara [an anti-IL 6 antibody] out, it was second to market. As such, we wanted to launch it at a price that was significantly lower than some of the alternatives. But our pricing efforts were handcuffed by a system that had contracts in place that were very difficult to unwind. So my question to Steve Miller and Jeff Berkowitz is: How do we move from where we are to a new world that allows examples like the pricing of Kevzara to happen?

*Though we must pause our most insightful drug-pricing discussion here, David Meeker's thought-provoking question primes the conversation to continue next month in, "Making Innovative Medicines Affordable: Concluding An Insightful Drug-Pricing Discussion — Part 2."*



**PIERRE LAURIN**
Founding Chairman & CEO
Prometic

THE
# ENTERPRISERS

*Life Science Leadership In Action*

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

# PROMETIC: New Tech Harvests Orphan Treatments

**PUBLIC COMPANY**

**MARKET CAP: $1.179B (IPO 1998 on TSX)**

**CASH: Proforma cash runway post Q2 2017 C$96M**

**STARTUP DATE: 1994**

**NUMBER OF EMPLOYEES: About 400**

**FOCUS: Plasma-derived and small molecule therapeutics for orphan conditions.**

Always stick with your original goals, even when you reap another, off-the-scale success. Like many biopharma companies, Prometic invented a novel technology platform, initially to make new medicines available to unserved populations. It never strayed from that path, but its platform proved to be enormously useful in many other ways. Thus, again like many biopharmas, Prometic came to straddle two sides of the business: as a technology supplier to other companies, and as a developer of its own original products, most of them for treating orphan conditions. It is impossible to discuss the latter without explaining the former, yet this story centers on the company's founding purpose — bringing those new treatments into being.

## FINDING METHOD

Prometic, born first of the academic world, began its business existence by the actions of Pierre Laurin, founding chairman and current CEO. As a pharmacologist looking to invest in a company, Laurin believed the industry could do a better job of producing pure, safe, and effective medicines. He became interested especially in blood fractionation, which had delivered plasma, albumin, and other vital blood products using a methodology devised by Dr. Edwin Cohn in World War II. Still in use as the primary means of fractionation worldwide, the Cohn method involves precipitating blood products in ethanol, a highly volatile substance requiring extensive safeguards in the multi-stage manufacturing operations.

The old method is also limited to the most abundant blood constituents, leaving many, scarcer but potentially useful substances in the waste products remaining after the process. It occurred to Laurin that, if those constituents could be recovered with a better technology, they could be developed as treatments for many patients who suffer rare diseases because their own bodies fail to produce those proteins.

In 1989, Laurin encountered ACL (Affinity Chromatography Ltd), then an early-stage spinoff of the U.K.'s Cambridge University. Through ACL, Cambridge had been looking for ways to commercialize a product of its research into "mimetics," or chemicals that could display "novel affinity ligands" mimicking those found on proteins. The general target at the time was protein purification, which resonated with Laurin's core idea.

"I wanted to invest in something less mundane than a drug-delivery system, but when the Cambridge scientists were explaining to me this technology, the only metaphor I could imagine was Velcro," he says, "It could have countless applications. But I was dead right and dead wrong — right that the technology worked and dead wrong that it would only take the money I had myself to put the project through. It became much bigger than I ever imagined."

Laurin ultimately gathered enough money to buy the Cambridge spinoff, refounding and relaunching the company as Prometic Life Sciences in 1994 and bringing it on the Toronto Stock Exchange in 1998. Because raising funds in Canada would be easier than in the U.K., the company opened operations in Canada, where it subsequently began producing its affinity filters. For the rest of the 1990s and into the 2000s, Prometic grew substantially with its technology business alone, though it experienced numerous business and financial setbacks, from small to large, along the way. At some point, it may well have looked as if the company had forgotten its original mission, to develop its own therapeutics, beginning with the rare blood constituents lost in the Cohn process. Then an angel arrived to show it the way.

In 2000, the company received a big boost in applying its technology to blood-borne proteins from an unexpected but not unlikely source. The American Red Cross approached the company with the aim of developing better ways to rid donated blood of impurities and infectious agents. It also saw the potential of Prometic's technology to extract valuable blood products too sparsely present in plasma to harvest by the old process. At first, the primary concern was ridding the blood and plasma-derived products of prions causing Mad Cow disease, but the subsequent extraction programs grew to include multiple contaminants and potential therapeutic proteins. The company also gained extensive new expertise and knowledge in proteomics as a result of the projects.

Two joint ventures with the American Red Cross helped the company scale up the mimetic plasma-screening and protein-extraction process to industrial levels in less than two years. In the wake of Hurricane Katrina in 2005, however, the U.S. Congress ordered the federally funded group to concentrate

solely on disaster relief and abandon all commercial development with companies such as Prometic. Loss of the Red Cross partnership was a major setback for the young company, after growing rapidly to hundreds of employees and multiple sites in the USA, the U.K., and Canada. It lost two major partners, one to bankruptcy, and it struggled to keep up its cash flow as it fought to secure its IP.

"If we had been private, this would have been a non-event — we would just find more money and go on," says Laurin. "But we're public, and therefore the perception was, 'This will never work, stop launch!' To the folks on the boat, it looked like it was sinking. But when we realized we were still on the surface, even more good people had joined our crew, and we sailed on. That was a proud moment. Scientifically, our job then was just to execute, but you need the right people on board to execute. You need smart people on board to execute. So that was the trick."

In fact, the Red Cross alliance had generated some valuable commercial products. After Prometic successfully resolved its patent litigation with a former manufacturing supplier and raised more funds, the company essentially came out of the crisis with a new business on its hands. Like companies many times its size, it restructured into four discrete business units, with several units dedicated to the supplier side and the Prometic Biotherapeutics unit developing drug products in Canada.

After Shire acquired BioChem Canada in 2001, Prometic hired many of BioChem's scientists for its nascent drug-development team. It was a pattern that would repeat; Prometic has made liberal use of partnering and acquisition to augment its expertise and technology for all of its businesses.

## BACK TO THERAPEUTICS

The first blood plasma-derived product in Prometic's therapeutics pipeline is plasminogen — now at the BLA (Biologics License Application) stage on the accelerated approval pathway with an indication for congenital plasminogen deficiency (CPD), and entering clinical development for wound healing. Normally produced by the liver, plasminogen circulates throughout the body and, when activated, becomes plasmin, a protein with a critical role in lysis (destruction) of blood clots and excess fibrin in the body.

Thus, as the company says, plasminogen is "vital in wound healing, cell migration, tissue remodeling, angiogenesis, and embryogenesis." When a stroke patient receives TPA (tissue plasminogen activator), for example, the body must have sufficient plasminogen to halt the TPA's clot-busting reaction before it causes massive bleeding. One of the target indications for Prometic's plasminogen product is for use with TPA. But first on the roster of goals: Some people are born without the ability to produce enough plasminogen, creating truly horrible symptoms such as lung and skin lesions, and plasminogen augmentation may also promote healing of especially stubborn wounds.

The plasminogen product has benefited from some extraordinary evidence. Laurin describes what happened when Dr. Sara Bein, a psychiatrist and CPD patient, received a dose of the protein: "Dr. Bein had gone through 106 surgeries for blood clots and fibrotic complications and had been near death three times in her life, and she's now 34. When she joined our Phase 1 clinical trial for plasminogen deficiency, she had only 67 percent lung function, with one lung collapsed, and she was scared. She took the first infusion, and plasminogen started traveling in the vein. Within minutes, she started having a coughing fit, and she spat out the fibrous tissue that was blocking her lung. With the before and after pictures, that was evidence extraordinaire for the FDA."

Indeed, the agency took a look at the Bein story and — after strong Phase 2/3 results as well — excused it from doing an additional Phase 3 efficacy trial. Perhaps the decision also helped accelerate the company's discovery of other potential indications for its plasminogen. "We had thought we were just dealing with congenital deficiency and that would be it; we'd move on to other things. But as we started meeting more KOLs in this field, the monster kept growing," says Laurin. Other plasminogen indications now under investigation include acute lung injury, diabetic wounds, and closed wounds in the ear.

The Phase 3 trial for CPD was exceptionally small, only 15 patients, which the FDA allowed because plasminogen is a well-characterized natural protein. The product's accelerated status also allowed the trial's use of surrogate endpoints, which would normally require a post-marketing Phase 3 trial within six years. The primary endpoint was at least a stable 10 percent rise in plasminogen levels in patients during treatment along with an observed reduction in symptoms; the secondary endpoint, 50 percent of the patients having 50 percent less lesions, one of the most common symptoms of the condition.

Following plasminogen, Prometic has a long list of plasma-derived proteins in the pipeline. Now in Phase 3 for treating primary immunodeficiency diseases (PIDD), intravenous immunoglobulin (IVIG) leads the pack, followed by others at the IND (investigational new drug) stage including fibrinogen for fibrinogen deficiency, alpha-1 antitrypsin (AAT) for AAT deficiency, and C1 esterase inhibitor (C1-INH) for hereditary angioedema.

## LARGE LEADS TO SMALL

In early 2000, Prometic added small molecule capability to its drug discovery and development organization, augmenting the plasma-derived therapeutics. It set up its therapeutics operations in the United States, counting on the usual practice of U.S. FDA approvals driving authorizations in other countries. Although it may seem odd for a plasma-extraction technology to lead into small molecule drugs, that is exactly what happened, Laurin explains:

"We make molecular ligands that mimic the protein-protein binding interaction. For a ligand to be commercially viable, it must have an ability to break that bond, allowing for the elution of the protein. When I first looked at our library of ligands, I realized that some of them bound so tightly that they would not allow the elution of the protein. We actually had a library of compounds with high affinity and binding tightly to protein receptors — exactly what one needs for effective drugs. The small molecule division was born."

At that point, Laurin began licensing rights to drug candidates to increase the depth of the pipeline. The portfolio now has candidates targeting fibrosis, autoimmune diseases, and oncology. The lead compound, coded PBI-4050, is in Phase 2 for metabolic disease, diabetes Type 2, and other conditions.

Laurin says the small molecule business is a separate division with its own research, development, and commercialization focus. "The IP is domiciled in the U.K., and is controlled by a sub-board of Prometic. Most of the R&D is commissioned to our research group in Canada, many of whom joined the company from BioChem."

Originally, the plasma and small molecule groups operated quite separately, but the common goal of therapeutics, pushed along with the progress of plasminogen, has increasingly united the two. "Our scientists are focused on the biology of healing, irrespective of the source of the drug," says Laurin. "Moreover, the clinical regulatory and medical affairs departments are driving the clinical development of all drugs irrespective of whether they are orally active synthetic pharmaceuticals or plasma-derived biopharmaceuticals. At this point, what matters more is the therapeutic expertise in specific medical fields. There is a growing understanding of the body's healing process developing within the research functions of the business. We are realizing that there are more and more reasons for the small molecule and plasma-derived groups to work together. The reality is that over time, using a combination of our therapies in certain conditions could be a very powerful solution to some major diseases."

Some of the therapeutics in Prometic's pipeline could enter large markets such as diabetes and cancer. How would that affect its rare-disease focus? "In two words, it won't!" Laurin says. "We are an orphan and rare disease business. It so happens that some of our products have promising results on major disease conditions. In these larger indications, we will partner with big pharmaceutical corporations as appropriate. Our own focus will be on marketing these smaller products ourselves, providing strong customer service to the patients we help."

Despite the background of far-spreading success on the technology side, the soul of Prometic seems to reside solidly in therapeutics. If the soul stays strong, the company may also succeed in bringing a whole new flock of wonders into the biopharma world. L

*Read our exclusive online sidebar explaining the technology platform behind Prometic's therapeutic in development.*


## STATEMENT OF OWNERSHIP

1 *Title of Publication:* Life Science Leader

2 *Publication Number:* 2161-0800

3 *Date of Filing:* 09/29/17

4 *Frequency of Issue:* Monthly

5 *No. of Issues Published Annually:* 12

6 *Annual Subscription Price:* $197.00/year

7 *Complete Mailing Address of Known Office of Publication:* 5340 Fryling Rd, Suite 300, Erie PA 16510-4672

8 *Complete Mailing Address of Headquarters or General Business Offices of Publisher:* Same

9 *Full Names and Complete Mailing Addresses of Publisher, Editor and Managing Editor:* Publisher, Jon Howland, 5340 Fryling Rd., Suite 300, Erie, PA 16510-4672; Editor, Rob Wright, same as above; Managing Editor, Angel Clark, same as above.

10 *Owner(s):* Richard J. Peterson, 5340 Fryling Rd., Suite 300, Erie, PA 16510-4672, Terence C. Peterson, same as above.

11 *Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages or Other Securities:* None

12 *Tax Status (For Completion by nonprofit organizations authorized to mail at special rates):* Not Applicable

13 *Publication Title:* Life Science Leader

14 *Issue Date for Circulation Data Below:* September 2017

15 *Extent and Nature of Circulation:* Average No. Copies Each Issue during Preceding 12 Months/ Actual No. Copies of Single Issue Published Nearest to Filing Date. A. Total Number of Copies: 27,011/28,146 B. Legitimate Paid and/or Requested Distribution: (1) Outside County Paid/ Requested Mail Subscriptions Stated on Form 3541: 25,122/25,197 (2) In-County Paid/Requested Mail Subscriptions Stated on PS Form 3541: 0/0; (3) Sales Through Dealers and Carriers, Street Vendors, Counter Sales and Other Paid or Requested Distribution Outside USPS: 551/665 (4) Requested Copies Distributed by Other Mail Classes Through the USPS: 119/64; C. Total Paid and/or Requested Circulation: 25,792/25,926; D. Non-Requested Distribution: (1) Outside County Non-Requested Copies Stated on PS Form 3541: 0/0; (2) In-County Non-Requested Copies Stated on Form 3541: 0/0; (3) Non-Requested Copies Distributed Through the USPS by Other Classes of Mail: 501/503; (4) Non-Requested Copies Distributed Outside the Mail: 550/1,550 E. Total Non-Requested Distribution: 1,051/2,053 F. Total Distribution: 26,843/27,979 G. Copies Not Distributed: 168/167 H. Total: 27,011/28,146 I. Percent Paid and/or Requested Circulation: 96.08%/92.11%.

# Importing Canadian Drugs Won't Solve U.S. Pricing Concerns

LARRY GORKIN, PH.D.

*In 2016, an estimated 19 million Americans purchased prescription pharmaceuticals from foreign sources through online pharmacies or while traveling, according to the Kaiser Family Foundation. Drug importation was driven primarily by pricing disparities, with Canada the country of choice.*

Ironically, among 35 members of the Organization for Economic Co-operation and Development (OECD) countries, only the U.S. and Mexico had higher patented drug prices as compared to Canada. In 2015, the U.S. was such an anomaly as to be 2.57 times greater than Canada in terms of average drug cost, according to a Health Canada analysis. The remaining countries in the OECD averaged 22 percent less in drug costs relative to Canada.

Although illegal, the FDA seemingly allows individuals to receive three months of prescription drugs for personal use. Several in Congress are calling for a formal change in FDA policy, legalizing the importation of prescription medications. The drugs would be purchased from a certified Canadian pharmacy with a valid prescription from a healthcare provider licensed in the U.S. When comparing prices in the U.S. and Canada, most senators contrast the cost of oral, primary care prescription drugs for diabetes, depression, etc. The price comparisons generally avoid specialty drugs, which are the cause of the double-digit increases in U.S. prescription costs over the past decade, according to a Kaiser Family Foundation analysis. These specialty drugs, defined as costing $670/month by Medicare, include an increasing array of injected monoclonal antibodies, indicated for cancer, rheumatoid arthritis, and recently to treat high cholesterol.

Specialty drugs, though, also include "old school" oral medications that arrive by mail from a Canadian pharmacy, including, ironically, drugs to treat cancer and rheumatoid arthritis. Regardless of administration, many of the specialty drugs cost more than $8,000 per month. The question raised is whether it is appropriate to look north to Canada as a realistic panacea for what ails America in terms of the pricing of specialty drugs.

The U.S. population in July 2016 was estimated at 324 million, whereas the corresponding Canadian population was 35.4 million. The U.S. population is over nine times greater than that of Canada. In terms of specialty drugs, such as those to treat cancer, the disparity is even greater. QuintilesIMS noted that the cost of global oncology therapeutics increased to $113 billion in 2016, with the U.S. responsible for 46 percent of total global oncology drug costs. In contrast, the U.S. accounted for only about 30 percent of the global pharmaceutical market in 2016, once the U.S. contribution was adjusted for increasing rebates and discounts (i.e., $323 billion/$1,105 billion).

Providing hope for Americans, Canada is rapidly increasing its use of specialty drugs, with only about 3 percent of drugs approved in the U.S. not approved in most provinces. In 2005, one novel drug was sold within Canada that cost between $20,000 and $49,999 per patient per year and two debuted at more than $50,000 per patient per year. In 2015, 45 new drugs were available in the $20,000-$49,999 segment, and 20 were launched in the >$50,000 category. In terms of cancer drugs, however, QuintilesIMS reported that only about two-thirds of drugs approved in 2011-2015 in the U.S. were available in Canada in 2016.

In Ontario, expenditure for oncology drugs, both intravenous and oral, was $652 million Canadian in 2014-2015, an increase of 20 percent relative to the previous year. Given that Ontario represents about 38 percent of the total Canadian population, this suggests that the entire oncology drug budget for Canada is about $1.72 billion U.S., adjusting for both a 20 percent increase in 2015-2016 and converting to U.S. dollars. Thus, the U.S. consumption of oncology drugs is about 30 times greater than that of Canada, more than three times the difference in population. These differences make it clear that the U.S. appetite for oncology drugs cannot be met by Canada. Ignoring pricing, Canadians should be the buyers rather than the sellers of oncology pharmaceuticals in relation to the U.S.

> *"The question raised is whether it is appropriate to look north to Canada as a realistic panacea for what ails America in terms of the pricing of specialty drugs."*

For some oncologists and senators, though, none of these statistics about the availability of oncology drugs in Canada seem particularly relevant to the argument advanced regarding drug importation into the U.S. That is, American patients should pursue oncology drugs in Canada, since even the lowest price in the U.S. is much higher than the corresponding highest price in Canada. The response to the shrinking of product in Canada is that large pharma will simply resupply Canadian shelves with drugs that Americans purchase from Canada. Let's provide an example for context:

### CASE STUDY: REVLIMID TO TREAT MULTIPLE MYELOMA

Multiple myeloma (MM) is the third most common blood cancer after lymphoma and leukemia, and an estimated 1,600 men and 1,150 women were diagnosed with the disease in Canada in 2016. The most successful therapeutic in the treatment of MM is Celgene's Revlimid (lenalidomide), which is a more potent molecular analog of thalidomide, which inhibits tumor angiogenesis. Thalidomide was launched in Canada and Europe in the 1950s, but not in the U.S., as an anti-anxiety agent. When prescribed to pregnant women, though, there is a six-day window in which the impact of thalidomide leads reliably to teratogenic or fetal abnormalities, including underdeveloped or completely absent limbs. The infamous drug led to millions of dollars in victim settlements in Canada and internationally. Although Revlimid does not appear to offer a survival advantage over the generic thalidomide, the former offers a preferred adverse event profile, that is, significantly lower rates of neuropathy.

Standard regimen for MM costs more when bortezomib and dexamethasone are combined with Revlimid. This regimen demonstrates an overall survival benefit over Revimid plus dexamethasone when tested on newly diagnosed MM. Average survival time increased from three or four years in the late 1990s to almost a decade currently.

Revlimid is increasingly being prescribed in Canada following the 2017 Health Canada approval of lenalidomide in combination with dexamethasone as a first-line treatment for MM patients who are not eligible for stem cell transplant. This subpopulation captures about two-thirds of newly diagnosed patients with multiple myeloma. An Express Scripts report indicates that Canadians spend more of their oncology drug budget on Revlimid, 15.7 percent, versus any other therapeutic agent. In Canada, Revlimid costs between $8,000 and $10,000 Canadian per month, depending on dosage. Express Scripts in the U.S. noted that Revlimid was the number one oncology drug in terms of 2016 spending, given a cost of $15,000 U.S. per month. There were greater than 30,280 new cases of MM diagnosed in 2017, according to the American Cancer Society.

Of the $6.97 billion Revlimid generated globally in 2016, Celgene did not provide the percentage registered in the U.S., except for the final quarter in 2016. That is, fourth quarter U.S. sales were $1.19 billion, whereas international sales were $621 million. Thus, nearly two-thirds of revenue was generated in the U.S., notwithstanding that the Kaiser Family Foundation reported that the median out-of-pocket cost for a Medicare patient on Revlimid was $11,538 in 2016, whereas the 2016 median annual income for Medicare beneficiaries was approximately $24,000.

If Americans were to purchase chronic therapeutics such as monthly Revlimid from Canada, MM patients could reduce their expected costs by about 50 percent, from $180,000 down to $90,000. In contrast, pharmaceutical manufacturers generate reliable prescribing models regarding how much drug a country uses annually, and projected growth rates based on the recent epidemiologic and pricing trends. Therefore, a particular country could receive a specified drug amount determined by these parameters plus a "fudge factor," for example, of 5 percent. Then the onus would be on the country, such as

Canada, to keep its supply of a drug (e.g., Revlimid for the care of MM patients) within Canada.

Companies want to limit the availability of specialty drugs in developed countries. To accomplish this, a second approach is utilized in terms of contracting agreements with less developed countries. For example, Gilead reportedly provides Egypt its curative hepatitis C treatment at a steep discount contingent upon strict procedures to keep the drug within the country.

The key question is whether Celgene would be willing to "toss away" these models and accept half the Revlimid revenue per American patient annually. Accordingly, the manufacturer would reliably refill pharmacies in Canada with Revlimid to supply the increasing American demand. Bear in mind that Revlimid represents about 62 percent of company revenue.

## EUROPEAN PARALLEL TRADE AS A MODEL

There is not an easy empirical comparison to make. Europeans have experienced parallel trade, both informally and formally for many years, but this circumstance may not be the same as what is being described in terms of a large-scale American importation of Canadian specialty drugs. Parallel trade tends to occur when a relative >15 percent disparity or 15-euro difference exists between the local price of a drug within an EU nation (e.g., Germany) and the price obtained by distributors bringing in drugs from a country (e.g., Spain) in which the price is lower, according to a 2017 QuintillesIMS analysis.

Germany formalized this practice in 2004, requiring that at least 5 percent of drugs sold be within the parallel trade paradigm. The impact was to generate increasing parallel trade in Germany from 2005 to 2010, but the effect has receded in more recent years. The QuintillesIMS analysis noted that the bulk of parallel trade involves nonspecialty oral drugs. In turn, recent reductions in parallel trade may reflect that the Germans have increased their share of more expensive, albeit rebated, specialty drugs.

Pfizer's oral antidepressant Zoloft (sertraline), rather than Revlimid, is the paradigmatic drug for parallel trade. If Zoloft normally would cost $2 per day in England, receiving a parallel trade version of Zoloft for $1.70 per day (15 percent reduction) or even for $1.00 per day (50 percent reduction, as in the Revlimid example for Canada vs U.S.) is not necessarily the same when applied to a drug which costs $180,000 and is available at either $153,000 or $90,000, respectively. That is, pharma companies' acceptance of parallel trade for low-priced drugs does not imply a corresponding acceptance when the paradigm is applied to high-priced drugs.

## THERE NEEDS TO BE A PARADIGM SHIFT

Given the low cost of manufacturing an oral medication, the profit margins for Revlimid are impressive at any of the prices cited. Arguably, a percentage of American consumers who could not afford the drug at one price point, but could afford it at another, creates a market at a lower price that wouldn't otherwise exist. Alternatively, manufacturers may not leave tens of thousands of dollars per patient "on the table" by replenishing Canadian pharmacies with specialty drugs to be bought reliably and on a large scale by Americans. These remain empirical questions.

An article by John McManus in the June 2017 issue of *Life Science Leader* seemed to capture the most often-cited criticism of Canadian imports: "Four former FDA commissioners — Democrat and Republican alike — agreed in a letter to Congress that importing drugs from other countries is not the right approach. The commissioners warned of serious risks to consumers and patients because these drugs can be counterfeit, substandard, and unsafe." For example, between April 2016 and March 2017, Health Canada seized nearly 5,500 packages of counterfeit drugs targeted for export. A representative valuation for one week's catch of counterfeit drugs was $2.5 million.

Of course, McManus' perspective and the one developed here are not mutually exclusive, and more rightfully may be viewed as complementary. The aim of this article is to establish that Canada is ill-equipped to supply sufficient quantities of high-priced specialty drugs that cause the most concern to financially strapped Americans, without a paradigm shift accepted and adopted by manufacturers. Without voluntary compliance by manufacturers, Canadian suppliers will not fill the demand for these specialty drugs. Given the potential for profits in the absence of manufacturer compliance, the vacuum generated is still likely to be filled with Canadian drugs exported to the U.S. However, these drugs will originate from a country other than Canada (with less valid regulatory oversight than Canada) or involve outright counterfeit supplies. Either scenario would be consistent with the McManus perspective presented in the recent *Life Science Leader*. Pricing concerns in the U.S. are likely to increase with these realizations regarding Canada. L

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# Value-Based Healthcare: Pharma's Role In The Transition

**CAMILLE MOJICA REY** Contributing Writer @CamilleReyATX

*This is the first in a two-part series on value-based healthcare. In Part II,* Life Science Leader *will look at value-based models used to determine the price of drugs.*

The U.S. spends more than any other developed country on healthcare, yet ranked 34th out of 163 countries surveyed as part of Bloomberg's 2017 Global Health Index. Despite the fact that we are obviously not getting what we pay for when it comes to healthcare, what we pay is expected to keep rising. The U.S. CMS reports that healthcare expenditures in 2015 were 17.8 percent of GDP, estimating a rise to 20 percent of GDP by 2025. Enter value-based healthcare, a concept introduced 11 years ago as a way of improving the health outcomes achieved from that spending. Today, a host of factors — including regulatory reform, rising costs, increasingly personalized medicine, and public demand for higher quality — have combined to move value-based healthcare from theory to inevitability. And, with the CMS reporting that prescription drugs account for 10 percent of our nation's healthcare spending, leaders in the pharmaceutical industry are among the stakeholders being called upon to participate in the transition from volume-based to value-based healthcare.

"The old way of doing things was focused on sales and marketing strategy and tactics to compete and drive sales," says George Serafin, national managing principal of Grant Thornton's Health Care and Life Sciences practice. "Value-based healthcare is really the premise that you are focusing more specifically on patient outcomes and, for the pharmaceutical industry, the value that your drug is providing from an efficacy and safety perspective." The high cost of healthcare, as well as public outrage over drug pricing as exemplified by the 2016 EpiPen controversial price increase, are calls to action for the pharmaceutical industry, Serafin says. The 2015 Medicare Access & CHIP Reauthorization Act (MACRA) made the transition to value-based care official, he adds. That's because MACRA changes the formulas that determine the way providers will be paid from volume-based to performance-based. Starting in 2019, the Merit-Based Incentive Payment System goes into effect. Providers will either gain or lose as much as 4 percent depending on their 2017 performance relative to peers, adjustments that will grow to as high as 9 percent by 2022.

And that's a good thing for healthcare consumers, says Elizabeth Teisberg, cocreator of the idea of value-based healthcare strategy. "We've changed the conversation. People are no longer only talking about what do things cost, but are paying attention to what are we getting for what we spend and whether we are helping people," says Teisberg, who is also executive director of the Value Institute for Health and Care at the University of Texas' Dell Medical School. Fifteen years ago, Teisberg says, the presumption was that all healthcare was good, and the care people received in the U.S. was better than anywhere else. "We now know that's not the case. Some of the healthcare you get in the U.S. is the best you can get in the world, and some of it is not." Increasing quality — as measured by outcomes — while reducing cost is at the heart of value-based healthcare and something, Teisberg says, the pharmaceutical industry has been analyzing for a long time. "They talk about pharmacoeconomics, and they are always asking themselves about the benefit of the drugs they are making relative to the cost of them. So, this is not a foreign approach for pharma, but it's important for us to start asking the question: 'What are the results being achieved for the money being spent in the delivery of healthcare overall?'"


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The pharmaceutical industry has more expertise in addressing questions of value than most in the healthcare industry because it is an industry focused on the collection of large sets of complex data, implementing protocols that improve outcomes, and measuring those outcomes. "Value in healthcare is created when someone's health improves. It is defined as the outcomes achieved for the money spent. You tend to get improvement in what you measure. So, if we are measuring the outcomes that patients achieve, we are more likely to improve that."

## CONTRIBUTE & COLLABORATE

The gathering and analysis of real world data (RWD) — generated during and after treatment — is something large drug companies are already good at and something that the pharmaceutical industry can contribute to the healthcare industry as a whole as it goes through this transition, Teisberg says. Pharma leaders like John Wise agree. Wise is the executive director of the Pistoia Alliance, a global nonprofit whose members include life sciences companies, vendors, publishers, and academic groups that work together to facilitate innovation in R&D. Alliance members already collaborate on precompetitive projects, sharing data and results aimed at moving the field as a whole forward. This is the kind of collaboration within the industry necessary to make value-based healthcare delivery a reality, Wise says. "Achieving the transformative impact of RWD requires companies to collaborate and ensure representation of this data in a 'common language' — to guarantee benefits for patients and payers alike, and facilitate safe, private, and sharable data that can ultimately deliver value-driven benefits across the board." The Alliance has set up a group to look at the development of such an RWD platform that will enable the shift to value-based healthcare delivery worldwide.

Collaboration between pharma and other sectors of the healthcare industry is also necessary. BIO's New Jersey affiliate is hosting its second annual Beyond Value Frameworks Workshop in December 2017. Members will hear from patients, regulators, payers, providers, and lawmakers. The idea is to facilitate cooperation among all stakeholders in the healthcare system. "The pendulum is swinging in the direction of collaboration," says Debbie Hart, BioNJ's founding president and CEO. Last year's inaugural workshop was intended to provide information, tools, and strategies for understanding and helping to shape value frameworks. The topics discussed included the importance and impact of engaging patients early on in the drug development process and incorporating patient preference, RWD, and long-term health improvements into pricing models. "Although the transition is happening slowly, payers are increasingly basing reimbursements on the quality of care provided, not just the number and type of procedures or medicines prescribed."

*"Most of this interest has been too focused on only one aspect of healthcare costs – the cost of biopharmaceuticals – causing us to lose sight of how all aspects of the system work together."*

**DEBBIE HART**
Founding President & CEO, BioNJ

According to Hart, the focus on drug pricing has been disproportionate to the contribution of prescription drug costs to the overall cost of healthcare. "As part of this transition, there is an increased interest in understanding how to measure value. Yet, most of this interest has been too focused on only one aspect of healthcare costs — the cost of biopharmaceuticals — causing us to lose sight of how all aspects of the system work together." Teisberg agrees that value is created holistically by the combination of efforts, pharmaceuticals, and other treatments. In value-based care, a person with diabetes will no longer receive disjointed care from a list of providers, including a primary care physician, endocrinologist, cardiologist, and dietician. Instead, the individual will receive care from an interdisciplinary diabetes team that might also include a pharmacist, diagnostics technician, physical therapist, and mental health professional. Care will be bundled in this way for a whole host of conditions, Teisberg says. The price of the pharmaceutical, then, will be paid within the bundle by the medical team. And decisions about which therapies, drugs, and techniques to use will be made by the team — by the experts working with the patient. This model isn't new. For example, bundled care and bundled prices have been used for years for patients who need organ transplants, Teisberg says. "Offering integrated care solutions — or care bundles — eases the transition to team-based payment. Paying for solutions aligns healthcare with its purpose of helping people." L


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# Why South Korea Is The Hottest Growth Spot For Clinical Trials

**ED MISETA** Chief Editor, Clinical Leader @EdClinical

*For any pharma company, the success of a study can often depend on selecting the right country in which to conduct a trial. Clinical experience, government regulation, and an accessible patient population are just a few factors that must be considered.*

One country that has recently experienced astounding growth in this area is South Korea. The country's mix of clinical experience, infrastructure, population density (50 million, with 25 percent concentrated in the Seoul metropolitan area), and a supportive government has boosted it into the top 10 locations worldwide to conduct a clinical study.

According to Deborah Chee, president of the Korean National Enterprise for Clinical Trials (KoNECT), sponsors like the speed and quality they get from performing trials in South Korea. The population density ensures a strong availability of patients, and the Korean healthcare system provides universal coverage via clusters of technologically advanced hospitals concentrated in large cities such as Seoul, Busan, and Incheon. The hospitals are monitored continuously by the government through accreditation and evaluation programs. "With 66 hospitals per million people, South Korea ranks second among OECD (Organization of Economic Cooperation and Development) members," says Chee. "Rapid recruitment and startup are enabled by optimized recruitment practices and the large volumes of daily patient traffic."

The numbers speak volumes about the growth of clinical trials in South Korea. For the past five years, Korea has conducted more industry-sponsored drug studies than any other Asian country, and the capital city of Seoul is now the world's top-ranked location for trials.

## 14 YEARS OF CONSISTENT GROWTH

Korea Good Clinical Practice (KGCP) was legislated by the country in 1995. In 2001, an amendment adopted International Council for Harmonization Good Clinical Practice (ICH GCP) standards. Chee states the growth of clinical trials in South Korea began to take off the following year, following the introduction of a new Clinical Trial Authorization (CTA) process. In just one year, the number of trials increased from 55 to 143. Four years later, that number hit 282. That is when the nonprofit organization funded by the Korean Ministry of Health and Welfare, KoNECT, was started to advance and promote the country's clinical trial capabilities

By 2008, the number of trials had climbed to 400. In 2012, South Korea performed 670 clinical trials, but kept pushing for even greater improvements. Over the next four years, it would open a Global Center of Excellence, start the Korea Clinical Trial Global Initiative (KCGI), and open a KoNECT Collaboration Center. The Collaboration Center is a one-stop shop for clinical trial planning, an open community for networking and business partnering, and a place to experience all of the capabilities of the Korean clinical trial industry. It also serves as a liaison with the country's clinical trial networks.

The therapeutic areas in which Korea performs trials are quite varied. In 2016, there were 200 oncology-related trials. Between 30 and 50 trials also were conducted in the cardiovascular, endocrinologic, central nervous system (CNS), gastroenteric, and antidiabetic areas. In 2016, most top pharma companies and CROs were conducting trials in South Korea, with Quintiles, Eli Lilly, PPD, Janssen, MSD (Merck & Co.), Novartis, and PAREXEL leading the way.

A readily accessible patient population is one factor giving the country a competitive advantage. As noted earlier, there is a high population density in the country. In fact, the population density is more than 15 times the average population density in the U.S. In addition to that, the country also has an aging population. With a citizen's life expectancy at birth of 81 years, Korea has

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> *"The Korean pharmaceutical industry has been accelerating investments in open innovation and focusing on R&D for entry into overseas markets."*
>
> **DEBORAH CHEE**
> President, Korean National Enterprise for Clinical Trials

one of the most rapidly aging societies in the world. The life expectancy has increased from 76 years in 2000, and is projected to increase to 82.6 years by the year 2020. The percent of the population aged 65 and older also increased from 7 percent in 2000 to 12 percent in 2016, and is expected to hit 15 percent by 2020.

What may make the population even more appealing to pharma companies is the fact that disease patterns in Korea are similar to those in Western countries. Korean patients also have similar unmet medical needs as patients in Western countries. Cancer is by far the leading cause of death, followed by cardiovascular disease and cerebrovascular disease.

Having an educated workforce to staff trial sites is another advantage. "Average student scores in literacy, math, and science make Korea's secondary education system one of the best in the OECD," states Chee. "Countrywide, 82 percent of adults 25 to 64 years of age have pursued post-secondary education, which is higher than the OECD average of 76 percent. Education is emphasized, particularly in the clinical trial sector where ongoing workshops and certification programs are held throughout the year."

In the country's hospitals, modern medical software is used extensively to enhance clinical trial efficiency and quality. Most hospitals have adopted electronic medical records (EMRs) and picture-archiving-and-communication systems (PACS). Major clinical trial sites are now using those EMRs to perform clinical trial feasibility assessments. "Hospitals in South Korea are also developing clinical data retrieval systems (CDRS) that enable queries of anonymous EMR data and assessments of pool sizes of eligible patients meeting specified inclusion/exclusion criteria," says Chee.

Currently, the list of the top 10 global clinical investigator sites includes four sites in South Korea. Those four locations (Seoul National University, Asan Medical Center, Samsung Medical Center, and Yonsei University Severance) have performed 2,258 studies in the past five years.

## SIMPLIFYING THE REGULATORY PROCESS

Carrying out clinical trials in other countries means having to deal with foreign — and often unfamiliar — regulatory authorities. Chee says the CTA process was put in place to foster faster study startup times, with the goal being to get trials approved 30 days from the date of submission. The Ministry of Food and Drug Safety (MFDS) then either approves the trial or issues a request for additional information. The procedure allows sponsors to simultaneously submit trial requests to IRBs (institutional review boards), ethics committees, and the MFDS, thereby reducing the time needed to get to approval.

This is an attractive proposition to pharma companies that continue to struggle with study startup, still seen as one of the most costly and time-consuming delays in clinical research. According to one company performing trials in Korea, the average time to start up is 152 days, whereas the average for the other 14 countries in the top 15 is 224 days.

All of these factors would not mean much if a country does not have experienced clinical trial personnel running quality studies. Looking first at experience, the number of trials conducted in Korea between 2011 and 2016 rank it number one in the Asia Pacific region, well ahead of Australia, Japan, and China. Korea also has the second lowest percentage of nonrecruiting sites at just 4.6 percent.

With its success in recent years, don't expect the growth in the Korean market to slow anytime soon. Today the Korean pharmaceutical market is estimated to be worth $19 billion annually and is expected to grow at an annual rate of 10 percent, surpassing the global average of 6 to 7 percent.

"The Korean pharmaceutical industry has been accelerating investments in open innovation and focusing on R&D for entry into overseas markets," adds Chee. "Those efforts encompass not only new medicines, but also platform technologies, medical devices, and incrementally modified drugs. Korea's MFDS has approved 26 new domestically developed drugs and boasts the world's first monoclonal antibody biosimilar [Celltrion's Inflectra]. We expect this growth to continue into the future." L

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# Diversification Relieves Funding Pressure For Small Pharma

**CAMILLE MOJICA REY** Contributing Writer @CamilleReyATX

*Chronic pressure is a way of life for those starting pharmaceutical companies. It's a life filled with rounds of funding, investor demands, performance deadlines, and possible compound failures. But what if the technology owned by a startup drug discovery company was suddenly in demand by some of the world's largest food and beverage corporations? What if that opportunity gives you the flexibility and time to conduct your research on your own timetable?*

That's what happened to the founders of North Brunswick, NJ-based Chromocell 15 years ago. Approached by the likes of Coca-Cola and Nestlé, the Chromocell founders decided to take advantage of the opportunity and enter the flavors business. That meant taking a unique, slow-and-steady approach to building their drug discovery company — one that has now paid off.

Chromocell, which has never raised money from outside investors, has entered into its first partnership with a Big Pharma company and, with that company, has begun its first clinical trials for a non-opioid therapeutic for pain. "We stayed true to our roots and continued to allocate some of our resources to developing early-stage therapeutics programs," says cofounder Christian Kopfli. The dual, or parallel, business strategy has worked in the company's favor largely because the flavors business is more stable and lower-risk than drug discovery. "In our case, the two really balance each other out. The income from flavors has given us a buffer and a resilience in challenging economic times," Kopfli says. For the first decade, the company focused on flavors. "The pendulum has now swung somewhat in the other direction. We're now about 50-50 in terms of resources devoted to flavors and therapeutics."

Today, Chromocell's flavor division, called FlavorHealth, is focused on commercialization and building a viable business-to-business operation. On the therapeutics side, the company's first lead compound, CC8464, is in Phase 1 clinical trials in collaboration with Astellas Pharma Inc. In September 2015, the company announced it had entered into a license and collaboration agreement for the development and commercialization of CC8464 with Japan-based Astellas. In October 2016, it announced the FDA had granted fast track designation to the development program. CC8464 is being developed for the management of neuropathic pain associated with idiopathic small fiber neuropathy and other peripheral neuropathic pain. In addition to CC8464, which belongs to a new class of nonaddictive analgesics, Chromocell has drug discovery programs in other chronic and acute pain states and orphan diseases.

*"Unlike many biotech companies that are virtual, we do 90 percent of our work internally."*

**TINA GARYANTES, PH.D.**
VP of Therapeutics
Chromocell

Chromovert, the company's high-throughput screening technology, was invented by Kambiz Shekdar while at The Rockefeller University. The technology allows

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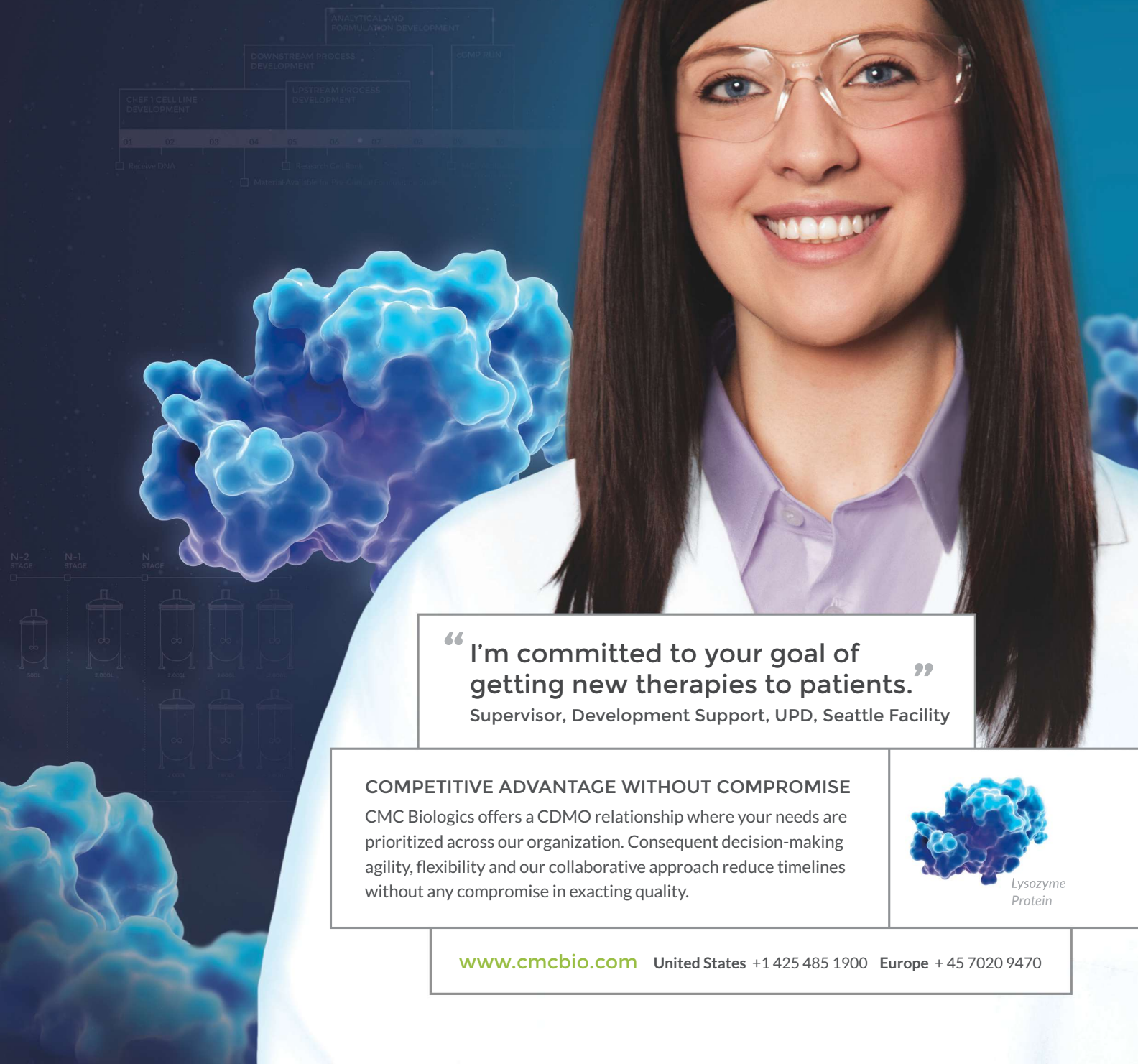


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millions of cells to be screened in the same amount of time it takes other systems to screen hundreds and thus allows Chromocell to create the best cellular models. Shekdar, who cofounded Chromocell, was the chief scientific officer of the company for more than a decade. He is now focusing on applying the technology to cell therapy.

Kopfli, who met Shekdar and became fascinated by the technology, is a lawyer by training with previous experience with VC firms and IPOs. As Chromocell's CEO, Kopfli says lacking a scientific background actually has its advantages. "I am not tempted to micromanage the science." Instead, Kopfli lets the research experts do their jobs. "I really focus my efforts on the big picture, working to influence strategy in terms of short-, mid-, and long-term goals."

## GROWING IN TANDEM

Having a CEO focused on the big picture seems all the more important when a business is essentially two businesses in one. The unique environment that creates has its benefits, as well as its challenges. Financing the company through collaborations not only means fewer sleepless nights for those who might otherwise be in charge of raising funds, but a steady pace to the science that is unusual in most pharmaceutical startups. "We have projects that simmer, and they bloom when there are opportunities and resources," says Tina Garyantes, Ph.D., Chromocell's vice president of therapeutics. Garyantes also says the years spent focusing on the flavors side allowed researchers to refine the company's technology.

Garyantes, who has been in charge of drug discovery and preclinical development for four years, says the company's structure also has allowed for an efficient use of resources. "Unlike many biotech companies that are virtual, we do 90 percent of our work internally." That's because while some employees are dedicated to either the flavors or the therapeutics side, many overlap as needed. "Often people have an extra hour in their day to contribute to a project on the other side, and that has made us very efficient." The therapeutics team was able to leverage resources on the flavor side and vice versa. "That made all the difference in our being able to partner with Astellas and get fast track approval from the FDA." In turn, the partnership with Astellas has allowed researchers to advance the rest of the company's therapeutic portfolio.

If there is a downside to the duality of the company, Garyantes says, it's that there are different expectations on the two sides. "Almost everything on the flavors side is expected to be natural. That's not the same on the therapeutics side. We have to reiterate that we are focused on what is viewed favorably by our potential customers." Despite these differences, she says, employees on each side of the business are quite similar. Food chemists, medical doctors, and pharmacologists have all managed to work well together in a company that is growing in two different directions.

> *"Until now, we did not have to do any financing, which gave us the flexibility, longevity, and patience to do what we believe in."*
>
> **CHRISTIAN KOPFLI**
> cofounder & CEO, Chromocell

As the therapeutics side of the company has grown, Kopfli says the question of whether the company will eventually split into two has come up. If it did, Chromocell would remain a drug discovery company, and FlavorHealth would become a sister company. But, Kopfli also says he believes in the old saying: "If it ain't broke, don't fix it." Flavors is now pivoting to commercialization, while therapeutics is split between bringing candidate therapeutics into the clinic and building a drug discovery pipeline. For now, the company will continue to take advantage of its unique ability to be active in two fields.

Kopfli says founders of young startup companies should explore the possibility that their company's technology might have applications in other fields. The traditional way of funding may not be the only avenue available. "Maybe you can create a business on the side or a parallel business that helps you grow. That might be something people should think about. Until now, we did not have to do any financing, which gave us the flexibility, longevity, and patience to do what we believe in."

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# Fostering Innovation Through A Diverse Workforce In Biotech

INGRID BOYES

*It's no secret that workforce diversity is not progressing as quickly as we once thought it might. Some areas have moved more slowly than others. We see that in politics and sports, banking and law. Hollywood's proverbial feet have been held to the fire because of it. And biotech is no exception.*

We are an industry steeped to its core in innovation, challenging the standards of healthcare to transform the future for patients. Achieving that requires us to embrace diversity in all its forms.

## DIVERSITY IN BIOTECH

Catalyst, a New York-based research and advocacy group for executive women, recently found that while women earned nearly 40 percent of undergraduate bioengineering and biomedical engineering degrees — and 38 percent of doctorates in those fields in 2011 — their educational achievements are not translating into top jobs. Women occupy only 20 of 112 senior management positions at the 10 highest-valued companies in the biotech industry. Furthermore, according to a study this year from British recruitment firm Liftstream, of the 177 biotech companies that went public between 2012 and 2015, women held only 11 percent of the board positions.

And yet, there is plenty of evidence that indicates the biotech sector would benefit immensely from instituting more diversity among leadership and in the workplace in general. A 2015 McKinsey study examined 366 public companies across industries in the United States, Latin America, Canada, and the United Kingdom. They found that companies in the top quartile for gender diversity are 15 percent more likely to have financial returns above their national industry means, and companies in the top quartile for ethnic diversity are 35 percent more likely to be above their national industry means. Moreover, companies in the bottom quartile for both gender and ethnicity were shown to be less likely than average companies to achieve better profits.

The study cautions that correlation is not causation; that it may simply be that whatever makes these companies successful is also what pushes them toward more diverse hiring practices. Whatever the case, it is inarguable that diversity is overwhelmingly an indicator of success for public companies, and not just something that we should want from a moral standpoint — but from a business standpoint as well.

## TECHNOLOGY'S BREAKING POINT

Our field can look to our colleagues in the Silicon Valley technology space, which has recently faced increased public scrutiny in this regard, as an example of how to begin to course correct. The diversity gap in the technology industry is wide, highlighted by poor findings in 2014 company surveys and bolstered by equally negative reports from the Equal Employment Opportunity Commission.

Despite these challenges, significant players are making meaningful changes. Recent diversity reports from major names in the technology industry such as Intel, Twitter, and Dropbox all show an improvement in this category. But the media had to criticize Silicon Valley relentlessly to force the hand of many of these companies, at which point business leaders in the technology industry had to scramble to save face. The biotechnology industry must take example from the technology industry and proactively address diversity issues in their own workplaces, before it becomes an issue that is much more difficult to address.

## DESIGNING EFFECTIVE DIVERSITY PROGRAMS

So what should a biotech company do if it wants to

improve diversity in its leadership (and its workplace overall)? It starts with the leadership. No matter how an organization approaches improving diversity, it is something leadership must be committed to in order for everyone to succeed. We need to empower those that understand the benefits of a diverse leadership, and establish a corporate mindset that values their various contributions.

Effective biotech companies are those that recognize true workforce diversity as a business imperative. Making bold changes to achieve that is a testament to organizational adaptability and it will naturally set you apart. However, biotech must take the right steps to ensure that employees across the enterprise are ready to embrace diversity in all of its forms. The companies with the most effective diversity programs take a strategic approach by following these guidelines:

- Make diversity unique to your organization. To be effective, diversity planning must be aligned with and provide support for strategic business objectives and operational decisions. Diversity should be linked to strategic plans and, therefore, unique to each company.
- Diversify now to stay ahead of the competition. Companies that adopt methods of diversifying their employee base now will benefit in the long run because it prevents an organization from becoming too insular and out of touch. They will be better enabled to stay competitive by anticipating and addressing the increasingly complex problems facing the biotech industry and the patients we serve.
- Cosmetic diversity is not enough. No organization can create meaningful change by filling quotas and complying with affirmative action initiatives. Diversity is about so much more. It's about creating an environment where people feel free to challenge the status quo, deliver new perspectives and solutions, and share success.
- Diversity is a state of mind. Listen and learn from those around you, and resist the impulse to follow a narrow, predetermined path to success. Actively include people who are different and employ a set of values based on mutual respect and constructive disagreement. Importantly, offer work/life flexibility to address the needs of a global, multigenerational workforce.
- Diversity is a journey, not a destination. Diversity management is complex, and not every company will advance at the same pace. It is a process of continuous improvement, which must be responsive to feedback from employees and other stakeholders.
- Facilitate employee connections to help unite a diverse workforce. No one wants to feel so unique that they're isolated from peers and lost in the workplace. It's equally important to provide resources for like people to connect as it is to celebrate diversity with team building activities.
- Harness the power of data to evaluate progress. Diversity strategies must contain well-defined metrics (e.g., linking to specific goals such as morale, retention, performance, and the bottom line) so that all employees and leaders clearly understand what is expected. Regularly assess progress so that changes are made quickly and accordingly to maximize effectiveness.

## KEYS TO STAYING COMPETITIVE IN BIOTECH TODAY

As our ambitions in biotech and the broader healthcare industry continue to grow, and we're faced with unique and complex challenges, it is imperative that our workforce reflects a level of thinking cultivated from the very best that human difference offers. We must understand that discrimination based on age, disability, gender, nationality, race, religion, and sexual orientation is not only ethically disastrous, but bad business. And the culture must be inclusive to unearth new ideas and advance research and development efforts, particularly in the era of precision medicine.

As research focuses more on understanding the genetic makeup that leads to diseases on an individual basis, the commonalities between the importance of diversity in biotech and advancing precision medicine cannot be ignored. They are both essential to stay competitive in biotech today, and they both have demonstrated that subscribing to a one-size-fits-all strategy is no longer relevant or effective.

I believe that diversity in the workplace will continue to foster innovation, and it will take us into the new frontier of discovering therapies that have the potential to impact large, underserved patient populations. But it is up to us at the center of the biotech industry to seize this extraordinary opportunity. If we can differentiate biotech from industries that still believe diversity is about head count and compliance rather than using diversity as a business strategy to solve business problems and contribute to business growth, we can set precedent and potentially even make history. L

**INGRID BOYES** is SVP of human resources for MyoKardia, a clinical-stage biopharmaceutical company focused on therapies for the treatment of serious and rare cardiovascular diseases. She has more than 20 years of human resources and senior leadership experience across the insurance, banking, and biotech industries.

# A Name Change — And More — For A Biotech

**CINDY DUBIN** Contributing Writer

*"I didn't come in to make changes to a business plan just for the sake of change. But in absence of a plan, I provided one for the organization," says Maria Fardis, Ph.D., MBA, CEO of Iovance Biotherapeutics, Inc. This is how Fardis explains her mindset a year ago when she joined Iovance, a biotechnology company developing novel cancer immunotherapies based on tumor-infiltrating lymphocyte (TIL) technology.*

With over a decade of experience in clinical trials and drug development, some of Fardis' past positions included COO of Acerta Pharma and chief of oncology operations at Pharmacyclics where she oversaw development of Imbruvica (ibrutinib). She says she starts any drug development program with the goal of getting a drug approved. "When you leave your house in the morning, you don't just drive and see where you end up; you drive with a purpose," she says. "All organizations should know where they are going and how to get there."

For Fardis and the management team at Iovance, that sense of clarity was being muddied by the company's previous name, Lion Biotechnologies. "The word 'Lion' didn't really define us as a company or the advancements we had made with our TIL technology," she explains. So, nine months into her tenure at Iovance, Fardis and the team began the process of changing the company name.

## WHAT'S IN A NAME?

A brand-development agency along with the company's internal legal group and management team spent approximately three months working through the creative process of selecting just the right name. Fardis explains that it was important the name not duplicate other company names or translate into anything offensive in other languages. Most importantly, the new name needed to convey the company's advancements in immuno-oncology (IO). Iovance's TIL technology is designed to address the manifold obstacles that attenuate the natural anti-tumor immune response. Dr. Steven Rosenberg at the National Cancer Institute (NCI) initially developed this approach, also known as adoptive T-cell therapy. Iovance's lead-product candidate is an autologous, ready-to-infuse cell therapy that has demonstrated efficacy in the treatment of metastatic melanoma. It is also being explored in squamous cell carcinoma of the head and neck, and cervical cancer. Additionally, TIL therapy technology is potentially applicable to other solid tumors. Studies are planned or underway in multiple tumor types such as lung, ovarian, glioblastoma, sarcomas, and pancreatic cancer. Thus, to show the company's advancement in the IO space, the name Iovance Biotherapeutics was selected and revealed to the public in June 2017.

## TRANSFORMING TECHNOLOGY & PROCESSES

"For the first time, through partnerships with CMOs, we have transformed the technology and process related to TIL manufacturing that was practiced in an academic setting and turned it into a potentially commercial process," explains Fardis. The initial academic process for preparation of TIL involved a number of complex manipulations. These steps were designed to provide frequent media exchange and determine if the quantity and quality of cells were ready to proceed to the next step. "We generated SOPs to limit the need for operators to perform multiple manipulations, thereby limiting variation in the process," she explains. "Our process has provided a streamlined method with a defined

schedule and a reduced number of interventions, therefore improving consistency while still maintaining the quality of the product. We send the work to a CMO to perform this robust process. TIL manufacturing is no longer just applicable in academic settings, and can be executed in a centralized facility with current good manufacturing practices (cGMP) consistently applied."

## CLINICAL TRIALS AND MANUFACTURING CAPACITY EXPANDED

Fardis believes this name change came at a pivotal time for the company. For instance, in Europe, Iovance is now working with the Karolinska University Hospital to support the generation of data on novel TIL preparations in treating pancreatic and glioblastoma indications. Clinical trials in Sweden with Karolinska, as well as trials in other European countries sponsored by Iovance, are scheduled to begin later this year. "Working with leading institutions in Europe and the U.S., Iovance has the ability to pursue a much broader clinical program than would otherwise be possible as a stand-alone company," she says.

Iovance also has entered into agreements to significantly increase production capacity that supports both late-stage clinical and, if needed, commercial demands. For the manufacture of cell-based products, the company has established multiple service relationships. These include providers such as WuXi AppTec, Lonza, and the Moffitt Cancer Center in the U.S. and PharmaCell in Europe. To enhance access to clinical data, new key partnerships were initiated with the Moffitt Cancer Center for clinical trials in melanoma and lung cancer to provide data on the combination of TIL and checkpoint inhibitor therapies, and the NCI for data on the combination of TIL with an anti-PD1 inhibitor in melanoma.

*"We do hope that the clarity that the new name brings will attract new investors."*

**MARIA FARDIS, PH.D., MBA**
CEO, Iovance Biotherapeutics, Inc.

To support an ongoing clinical trial that combines TIL therapy with nivolumab for the treatment of patients with metastatic melanoma and non-small-cell lung cancer, Iovance announced Clinical Grant Agreements with the Moffitt Cancer Center. A three-year Sponsored Research Agreement with Moffitt is also exploring the development of new TIL technology in a preclinical setting.

The company also established a clinical collaboration with MD Anderson Cancer Center this past April for access to rare patient populations with sarcomas, and clinical evaluation of TIL in ovarian and pancreatic cancer. This partnership also will explore a new method of manufacturing TIL using an MD Anderson process. The process of TIL generation at MD Anderson is slightly different from what Iovance utilizes. An additional co-stimulant is added to the media to assist in growth of TIL for certain tumor types.

Iovance recently initiated Phase 2 clinical trials for LN-145 in head and neck and cervical cancers, and the first patient was dosed in June. The company plans to continue enrollment in an ongoing, expanded Phase 2 trial for LN-144 (its lead product candidate) in melanoma. The melanoma studies conducted at NCI have showed an overall response rate of 56 percent in a broad patient population and a complete response rate of 24 percent in patients treated with TIL. Anticipated regulatory milestones include defining the pathway for LN-144 in the U.S. and the initiation of regulatory interactions with EU health authorities.

"By year-end we may have partner-sponsored trials in pancreatic, glioblastoma, ovarian cancer, various sarcomas and melanoma combination trials with three of the approved checkpoint inhibitors in addition to the three ongoing Iovance-sponsored TIL clinical studies in metastatic melanoma, head and neck and cervical cancers," Fardis says. "This gives us a robust pipeline based on our TIL technology."

## IT'S OK TO PARTNER WITH BIG PHARMA

As a clinical-stage biotechnology company, Iovance held $147.2 million in cash and cash equivalents and short-term investments at the end of March 2017, compared to $166.5 million as of December 31, 2016. "While investors make their determination about a company regardless of a name, we do hope that the clarity that the new name brings will attract new investors and provide us better visibility as a player in the IO space," says Fardis.

She sees obtaining regulatory approval as a barometer for success in drug development, but small companies only can go so far and may need help with that process. While Iovance continues to execute development of TIL in multiple indications in the U.S. and prepares for global trials, a partnership with Big Pharma would be considered great success as the product can benefit from broader available resources. Fardis says: "Success in drug development is bringing a product to the market, whether it is done as a stand-alone company or through partnerships with major pharmaceutical companies." L

# After The Failed Trans-Pacific Partnership: **What Comes Next?**

JOSH RICH

*The Obama Administration, seeking to expand international trade, negotiated the Trans-Pacific Partnership (TPP) with 11 other Pacific Rim countries. After President Trump assumed office in January, he immediately withdrew the U.S. from the multilateral agreement. The other TPP countries — now known as the TPP 11 — and other Asian countries have since been seeking a replacement low-tariff trade market.*

There are two approaches currently being pursued: a version of the TPP without the U.S. and the Regional Comprehensive Economic Partnership (RCEP) being driven by China and India. Under the former approach, the member states may maintain the intellectual property and other protections that the U.S. had demanded for the TPP; in the latter, many of them are likely to disappear.

## PUSHING FOR PHARMA IP PROTECTIONS

The TPP was negotiated by 12 countries along the rim of the Pacific Ocean: Canada, the United States, Mexico, Peru, and Chile in the Americas; Japan, Malaysia, Singapore, Vietnam and Brunei in Asia; and Australia and New Zealand in Oceania. American negotiators pushed for the inclusion of, among other things, strong intellectual property protections that benefit pharmaceutical and life sciences innovators. Many of those provisions sought to bring other member states' laws more closely in line with U.S. law: The treaty parties would have been obligated to amend their intellectual property laws to conform to their treaty obligations under the TPP.

Among its key terms, the TPP agreement addressed patents, trademarks, copyrights, and trade secret protections. TPP member states were required to meet the minimum standards set forth in the agreement, but were permitted to provide greater intellectual property protections (as long as they did not discriminate between the rights of domestic parties and the rights of citizens of other member states).

With regard to patents, members were to agree to grant patents to any invention that is "new, involves an inventive step, and is capable of industrial application." That would include new uses for known products, new methods of making known products, and new methods for using known products. TPP also sought to get rid of a requirement for "absolute novelty": Public disclosures by the applicant itself less than 12 months before the filing of a patent application would not constitute invalidating prior art. After filing, there would have to be patent term adjustment for any unreasonable delay in issuance of a patent (more than five years after filing or three years after request for examination), patent term extension for unreasonable delay in marketing approval, and substantial data exclusivity for agricultural chemicals, pharmaceutical products, and biologics. The exclusivity would be at least 10 years for agricultural chemicals, at least five years for a new chemical pharmaceutical entity, at least three years for a new indication for an existing pharmaceutical, and at least eight years for a biologic.

For trade secrets, among other things, the TPP would have required member states to adopt a law that would criminalize misappropriation.

With regard to copyrights, members would be required to establish a term that would extend at least 70 years after the death of the author or 70 years after publication, depending on the regime selected by the member state. However, the agreement would establish a safe harbor from copyright infringement liability for

**12** COUNTRIES ORIGINALLY PART OF THE TPP

AMERICAS - Canada, The United States, Mexico, Peru, Chile
ASIA - Japan, Malaysia, Singapore, Vietnam, Brunei
OCEANIA - Australia, New Zealand

**11** COUNTRIES MOVING FORWARD WITH THE TPP

AMERICAS - Canada, Mexico, Peru, Chile
ASIA - Japan, Malaysia, Singapore, Vietnam, Brunei
OCEANIA - Australia, New Zealand

**471,175,116**

COMBINED POPULATION OF THE TPP 11, AS OF 2016
(pulled from worldbank data)

**16** COUNTRIES THAT COULD POTENTIALLY BE PART OF RCEP, IF THE TPP 11 DOES NOT REACH AGREEMENT

Australia, Brunei, Cambodia, China, India, Indonesia, Japan, Laos, Malaysia, Myanmar, New Zealand, The Philippines, Singapore, South Korea, Thailand, Vietnam

internet service providers under certain conditions. All in all, TPP would require member states to have intellectual property protections built on a framework very similar to the regime that already exists in the U.S.

### SHORTER DATA-EXCLUSIVITY PERIODS FOR DRUG DEV DATA

At the conclusion of the most recent Asia-Pacific Economic Cooperation (APEC) meeting in May, the TPP 11 announced that they were moving forward expeditiously with a trade bloc based on the original TPP structure. According to some member state representatives, the TPP 11 is seeking to conclude their agreement by the end of the year, which would minimize the changes from the original text. However, there are likely at least some differences from the TPP, most notably, shorter data-exclusivity periods for drug development data. As the negotiations proceed, we will see how the member states balance their interests and if they can reach agreement on both intellectual property protections and tariff schedules. One caveat exists, however; just as with the TPP originally, the protections of any agreement by the TPP 11 would likely extend only to member state companies. As a result, U.S.-based companies would not necessarily profit from the agreement.

### INDIA OPPOSING PHARMA PATENT PROVISIONS

If the TPP 11 cannot reach agreement, or if they do not wish to adopt the entirety of the TPP framework, they may instead seek to join the proposed RCEP. The RCEP is expected to include all seven of the Asian and Oceanic states in the TPP, plus China, India, South Korea, Laos, Myanmar, Indonesia, the Philippines, Thailand, and Cambodia. During the negotiation and finalization of TPP, RCEP was kept on the back burner as a lesser, Chinese-led alternative. With the TPP losing steam in the U.S. at the end of 2016, the two South American TPP countries (Peru and Chile) expressed a desire in potentially joining RCEP. Thus, RCEP might end up an alternative to TPP for all but the three NAFTA countries.

Although the RCEP is still being negotiated — and its terms are not only still in flux but also generally secret — it likely will include certain intellectual property and privacy protections. Leaked drafts have shown that some of the intellectual property-owning countries (such as Japan, South Korea, Australia, and New Zealand) have sought intellectual property protections similar to those in TPP, albeit not as strong. However, given the fact that China would replace the U.S. as the largest market in the free-trade zone, and China itself does not protect intellectual property and privacy as strongly as the U.S. does, RCEP is less likely to require the strong intellectual property and cybersecurity provisions that TPP did. And India — the other large non-TPP market in the RCEP— opposes some of the TPP's intellectual property provisions even more strongly, especially the pharmaceutical patent provisions. Most importantly, India would like to protect its burgeoning pharmaceutical market by eliminating the requirements for patent protection on new uses for existing products (which many there consider "evergreening"). Thus, the strong intellectual property protections sought by the U.S. in the TPP would likely be watered down substantially in the RCEP. Furthermore, even those protections would not necessarily extend to U.S.-based companies; only RCEP-based companies would be guaranteed their protections.

Despite the Trump administration's withdrawal from the TPP, the other member states are going forward with a low-tariff marketplace. We should soon see the results of the negotiations regarding the marketplace. Unfortunately for U.S.-based life sciences companies, however, the marketplace's intellectual property protections will likely be less robust than they would have been under the TPP. L

JOSHUA RICH is a partner with McDonnell Boehnen Hulbert & Berghoff LLP and serves as chair of the firm's Trade Secrets Practice Group. He has more than 20 years of experience litigating intellectual property cases.

# Can AI Deliver Faster, Better Drug Development?

**NANCY LAMONTAGNE** Contributing Writer

*As the cost of developing new medicines continues to rise, more pharmaceutical companies are looking at how artificial intelligence (AI) can help in drug development. Although a handful of projects and collaborations are seeing important successes in applying AI to drug development, there are some hurdles to overcome before its full potential is reached.*

AI approaches use complex computer algorithms to quickly analyze large datasets. In the pharmaceutical industry, AI is combined with knowledge from experienced drug development experts and biological approaches for screening candidate molecules or creating and testing information that will be fed into the algorithms. This approach can provide insight into which molecules are most likely to show effects, biological pathways that make the best targets, and even which patients will respond to a drug.

Pamela Spence, global life science leader at Ernst & Young, says that AI's biggest payoffs will be in its ability to make drug development faster and more efficient and to create drugs with more precision and efficacy in the patient groups for which they are designed. "We are in AI's infancy," she said. "Because the typical drug development cycle takes 15 years, even if that is halved with AI, it will still take seven years to prove the merits of AI in drug discovery."

## COLLABORATION IS KEY

Spence says that to reap the most benefits from AI, pharma needs to seek innovative ways to collaborate with AI companies and build new business models that offer a marriage of equals. This could involve, for example, collaborating around the development of a new drug, which not only increases knowledge sharing but also distributes risk. Also, pharma should look for AI partners with data scientists who work very closely with biotechnology scientists, because this combination will produce the best cross-fertilization of ideas and progress.

"Pharma doesn't currently have all the skills needed to adopt AI successfully in an impactful, sustainable way, so they need to collaborate," said Spence. "It can be hard for pharma to work with high-tech companies, because pharma typically moves slowly and cautiously and is fearful of regulation, while the tech industry moves at a very fast pace and is almost fearless of regulation. This is a big cultural barrier to overcome."

Most AI algorithms need a great deal of data to find meaningful patterns. Not only must the data be high quality, but it should also include information from failed drugs or failed approaches. "It is going to take longer to innovate with AI if we don't make sure that we are transparent with what doesn't work as well as what does work," said Spence. "Culturally, we don't like to share and publicize what doesn't work, so pharma needs to figure out a way to share negative outcomes as freely as positive outcomes."

It is also important that AI approaches focus on the right drug development problems. Many drugs fail during clinical trials, after years and sometimes millions of dollars have been spent on development and testing. Spence points out that because these failures often result from developing a drug molecule for the wrong biological target, AI efforts that improve target identification at the beginning of drug development will have the largest impact on the industry.

In the long term, Spence sees AI as being particularly beneficial to the aging population. "With more

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impactful medicines, it could be possible to keep people healthy for longer," she said. "Ultimately, not only could AI get the right medicines to the right people at a cheaper cost, it could also help turn the aging society into an asset rather than a long-term cost."

## OPTIMIZING CANDIDATE MOLECULES VIA AI

There are a variety of places in the drug development cycle where AI can bring improvements. AI company Exscientia Ltd. applies its algorithms to designing the drug itself. Andrew Hopkins, the company's CEO, says that by using AI to identify the fewest number of compounds necessary to synthesize to go from the hit molecule to the candidate medicine, pharma companies can experience dramatic (e.g., up to 75 percent) reductions in the cost and time involved in drug discovery compared to conventional approaches. These savings can be used to take more molecules to clinical trials or put more resources into profiling the molecules and understanding the deep biology of how those molecules affect a biological system. For example, Exscientia is working with GSK on improving performance efficiencies in the pharma giant's drug design cycle.

"AI isn't just about having a technology platform, it's about combining it with human skills and using that to create a new drug discovery process that is superior to what is currently done," said Hopkins. "It's important for pharma to understand that this new process creates an entirely new way of working."

Exscientia is also working with Evotec AG to explore bispecific small molecules that can affect two targets or two pathways to potentially bring additive or synergistic benefits. For this type of application, the company uses known pharmaceutical data from journals, patents, and proprietary data from collaborators to seed AI algorithms.

According to Hopkins, many drug molecules selected with traditional approaches don't have enough firepower to be successful. However, designing drugs that perturb two pathways or two points in a pathway can sometimes increase the clinical efficacy of a drug by creating a double biological effect. Bispecific molecules can also tackle complex biological problems. For example, a diabetes medicine might be designed to not only lower glucose levels but also treat a comorbid condition such as heart disease. Sanofi has taken interest in this idea and recently signed an R&D partnership with Exscientia.

## RESCUING FAILED DRUGS

Lantern Pharma uses AI to rescue failed anticancer drugs by identifying patients who would respond to those drugs. According to Arun Asaithambi, founding CEO of Lantern, each new cancer drug that gains federal approval takes 10 to 12 years and costs about $2.6 billion to develop and test. However, about 90 percent of cancer drugs fail during clinical trials.

"There are really good drugs that don't show positive effects in enough patients to move forward in clinical trials, even though a lot of patients benefited from the drugs," Asaithambi said. "We identify the genetic signature of patients who responded to this drug and then use that to screen for patients to enroll in a prospective clinical trial. This precision medicine approach allows us to bring shelved drugs to the market quicker and to save on costs, compared to a traditional drug development process."

*"Pharma needs to figure out a way to share negative outcomes as freely as positive outcomes."*

**PAMELA SPENCE**
Global Life Sciences Leader, Ernst & Young

Lantern is currently applying its approach to two shelved anticancer drugs and has ambitious plans to put 25 to 50 drugs through its pipeline in the next five years. One anticancer drug already made it through the pipeline. In about 1.5 years, Lantern was able to identify the right patients, run the Phase 2 clinical trial, and then out-license this drug.

"There have been tremendous advances in terms of drug design, but the ability to choose the right patients for a trial has not kept up with those advances," Asaithambi said. "Four years ago, when I founded the company, we understood that precision medicine was going to be the future."

The Lantern AI platform involves analyzing clinical trial data from all currently approved cancer drugs as well as information from failed drugs. The information learned through this analysis is then tested in the lab using human clinical samples and tumor cell lines that model the cancers, ensuring that only biologically meaningful data is fed into the AI algorithms. Lantern's machine-learning algorithms automatically identify patterns to break down those billions of data points into meaningful molecular markers that identify the genetic signature for people who respond to the drug.

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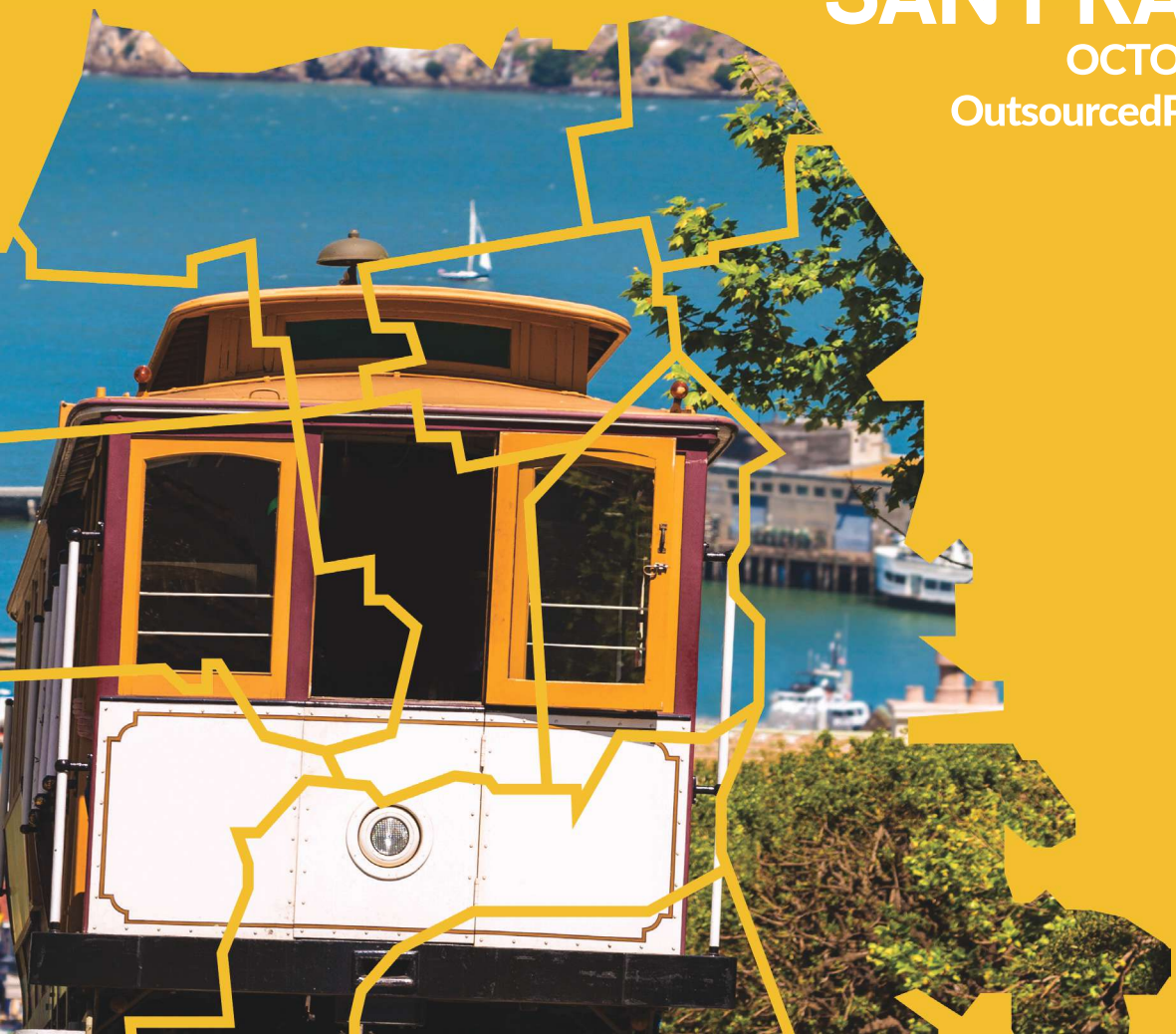


# How Innovative Organizations Think: Why Rules Matter

LINDA HILL

LINDA HILL is a professor at Harvard Business School and the coauthor of *Collective Genius: The Art and Practice of Leading Innovation.* In 2015, she received the Thinkers50 Innovation Award.

Innovation and rules may seem like an odd couple. Aren't innovators rule breakers, people who are willing — even eager — to challenge the status quo? For the most part, they are. Yet innovations rarely result from a genius having a single flash of insight. Instead, they emerge from a collaborative process of individuals with diverse perspectives generating a portfolio of ideas, testing and refining them, and finally, choosing a solution — most often one that combines seemingly competing ideas. Heated debate and conflict are a necessary part of cocreating the new — and as any leader knows, it can become hard for the group to bear. So how do innovative teams ensure this competition of ideas remains constructive, instead of devolving into chaos? They tend to follow three "rules" of innovative thinking: They question everything, they are driven by data, and they aim to see the whole.

## WHY DO GROUPS NEED "RULES" FOR THINKING?

In *Collective Genius: The Art and Practice of Leading Innovation,* we distilled more than a decade of research about what leaders do to build innovative organizations. Their priority: creating the culture and capabilities required to support the hard work of innovation — including embedding norms or "rules of engagement" that govern how the group thinks about and solves problems.

## QUESTION EVERYTHING

Innovative groups consciously question everything — especially the status quo. Instead of declaring certain practices, policies, ideas, or assumptions off-limits, they embrace lively inquiry and even friendly skepticism. The leaders we studied told us that this practice not only animates discovery, but helps them attract top talent — people who approach problems like intrepid explorers enjoy working with others who challenge conventional wisdom.

## BE DATA-DRIVEN

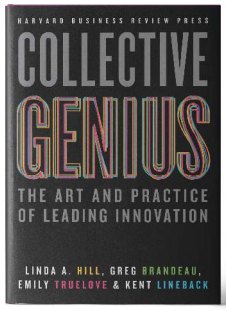
Innovative groups consistently pay attention to data. They voraciously collect and analyze information of all kinds: cost figures, test results, customer feedback, retention statistics ... you name it, they want it. Since innovative solutions often result from a process of trial and error, these groups crave quantitative or qualitative metrics to give them feedback on what is (and isn't) working.

If this sounds obvious, think about how often groups make decisions *in spite of* hard evidence simply because they believe the evidence doesn't apply to them, see the data as flawed, or don't want to face what the data is telling them. This refusal to face facts limits discovery.

## SEE THE WHOLE

Innovative groups maintain a holistic view of problems. It is easy — and only human — for individuals to focus on one part of a problem, rather than seeing how the parts fit together. But the best solutions often combine disparate elements, which can be appreciated only by understanding the whole picture, including connections, interdependencies, and patterns. These practices allow teams to see problems within a broader context or from multiple perspectives.

Our current research suggests that embedding these norms is one of the hardest but most important things for leaders to do. Taken together, these rules keep team members focused on what is most important, discourage unproductive behaviors, and encourage activities that foster collaboration, discovery-driven learning, and integrative decision making.



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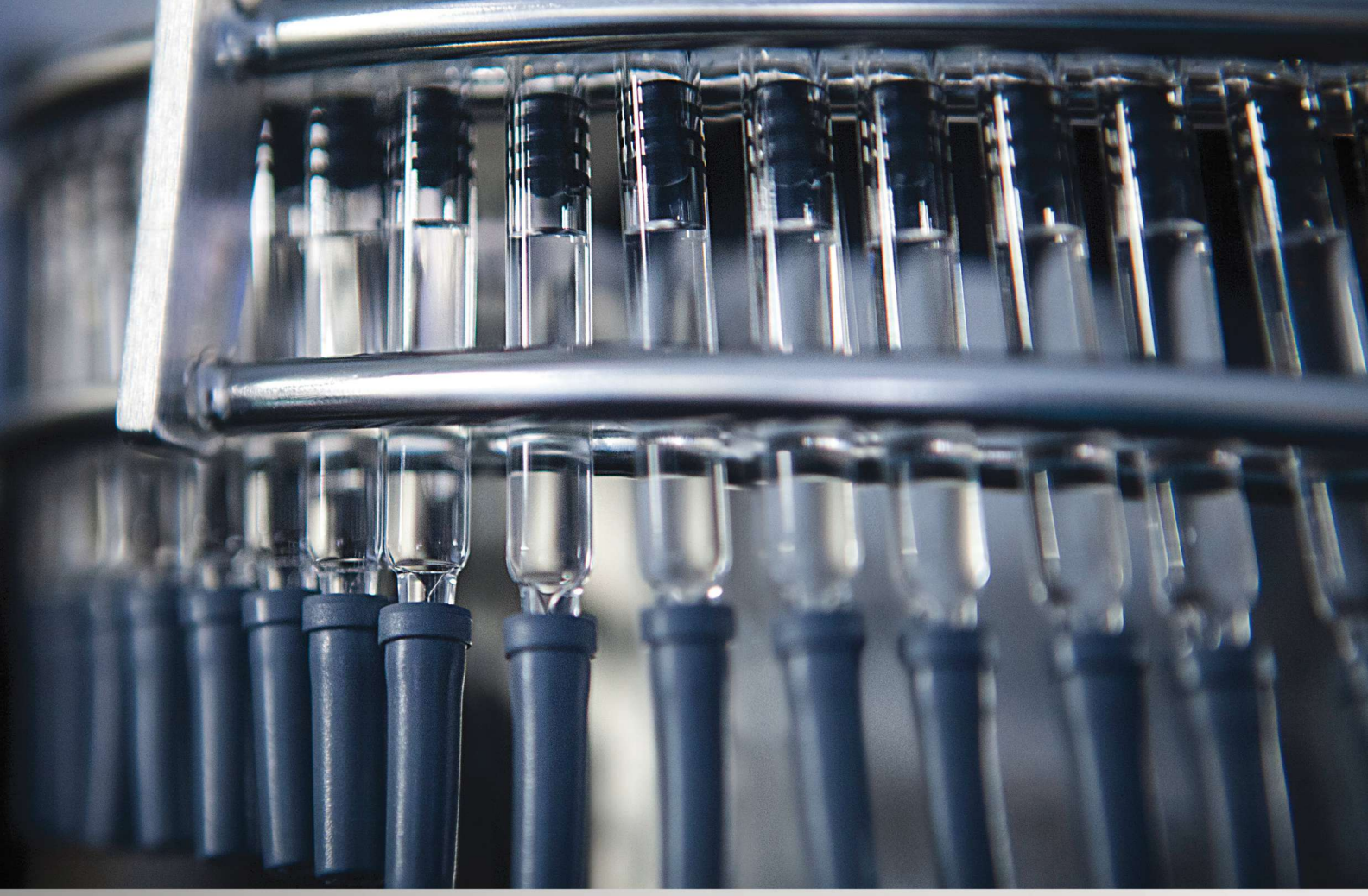

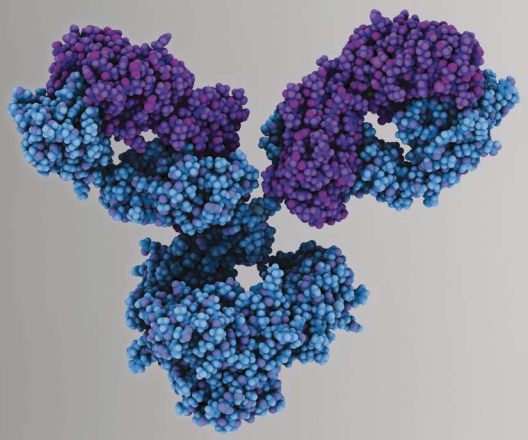

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