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JANUARY 2017

Janssen Immunology

Science & Market Drivers

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SUE DILLON, PH.D.
Head of Janssen Immunology

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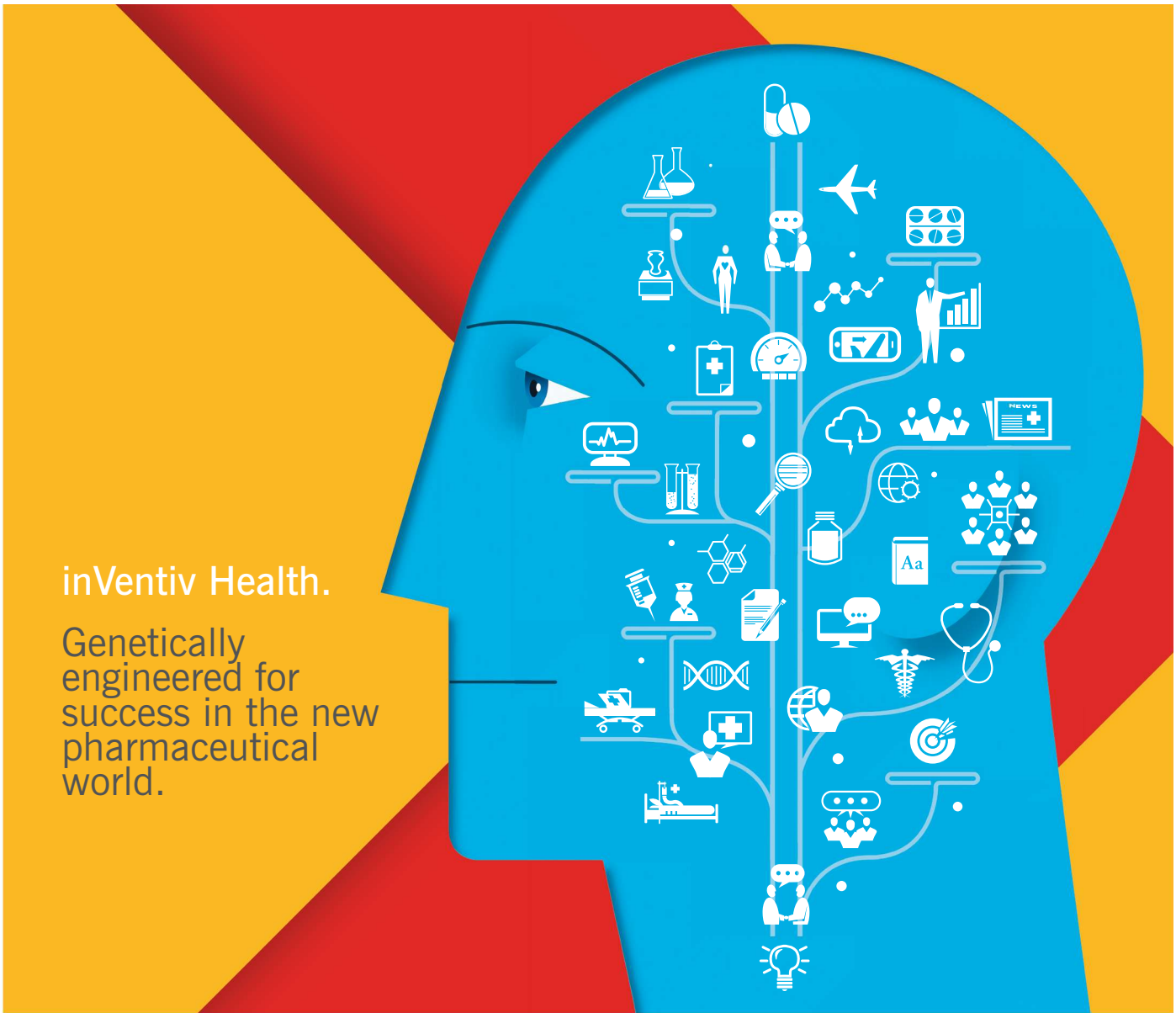

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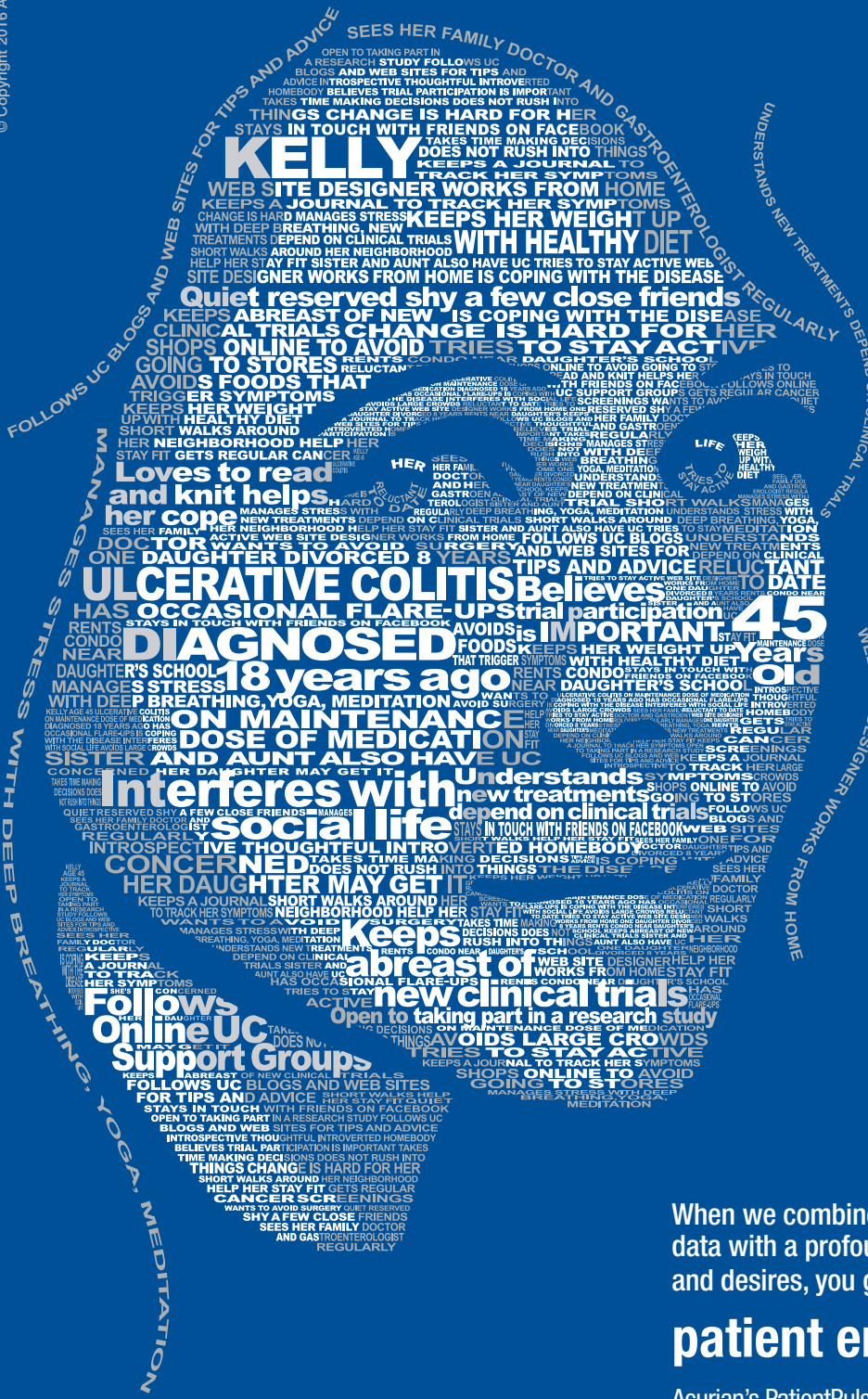

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What You Need To Know
About Being Ready To Join A Board

ROB WRIGHT Chief Editor

Last month I moderated a panel entitled, "Seeking A Board Seat." Hosted by BioBreak in Philadelphia (a nonprofit organization that brings together senior executives from across the life sciences and venture capital industries), the goal of the discussion was to help executives not only figure out how to get selected for board of director positions, but also to determine which companies might be a best fit. During Thanksgiving dinner, I was describing the upcoming panel's concept to my brother-in-law. He commented, "I thought companies picked the people who they want for their boards." While true, this doesn't mean you should just sit back and wait for the phone to ring. Conversely, you shouldn't necessarily start reaching out to companies on an unsolicited basis. Serving successfully on a board typically requires the application of your acquired leadership skills in a slightly different capacity (i.e., more as a consultative guide). So if you think you are ready to join a board, before doing anything, you should first do a self-assessment.

According to industry icons Fred Hassan and Ken Banta, company boards primarily look at these two criteria: capabilities and character. As such, begin your self-assessment by looking at your capabilities and try to determine your special skills. For example, when Hassan was asked to join Time Warner's board, it wasn't because he had a deep understanding of the media and entertainment industry. He was invited (in large part) because his expertise in the regulated realm of healthcare could be applied to the increasingly regulated world of global telecommunications. Assess yourself not only as a sector expert but also as an executive with special competencies. Then map these attributes against various market needs. Next, compare yourself with other executives based on your proven track record. Hassan and Banta suggest engaging colleagues and mentors for help.

Regarding the character component of board selection, there are five areas where you will need to demonstrate special strengths: collaborating, earning trust, emotional intelligence, judging others, and raising questions. Identify moments in your career when you exemplified these character components and list examples that demonstrate your leadership success as a result of their application. Unlike most executive roles where leading involves a lot of "telling," board members typically succeed by asking. According to Hassan and Banta, by asking thoughtful questions you will be better able to guide a CEO and other board members toward making good business decisions.

Shortly after Leonard Jacob, M.D., Ph.D., left his position as chairman of the board for Bradley Pharmaceuticals (2006), he was asked to serve as board chairman for Antares Pharma. Although he did review the company's financials and the management team, he admits the first thing he looked at was the product opportunity. Thus, he advises that anyone considering serving on a board review the product first *and then* the leadership.

If you have not served on a board, David Pyott (former CEO of Allergan) says likely the first call you'll receive will come via an executive search firm. As such, he says to make it known to firms specializing in board placement that you are interested, and provide criteria on industry preference, as well as geographic location. Finally, while serving on a nonprofit can be a great place to gain some board experience, consider reviewing Shelly Banjo's *Wall Street Journal* article "Before You Join That Board..." so you can sufficiently weigh prestige and honor versus the commitment such service entails. L

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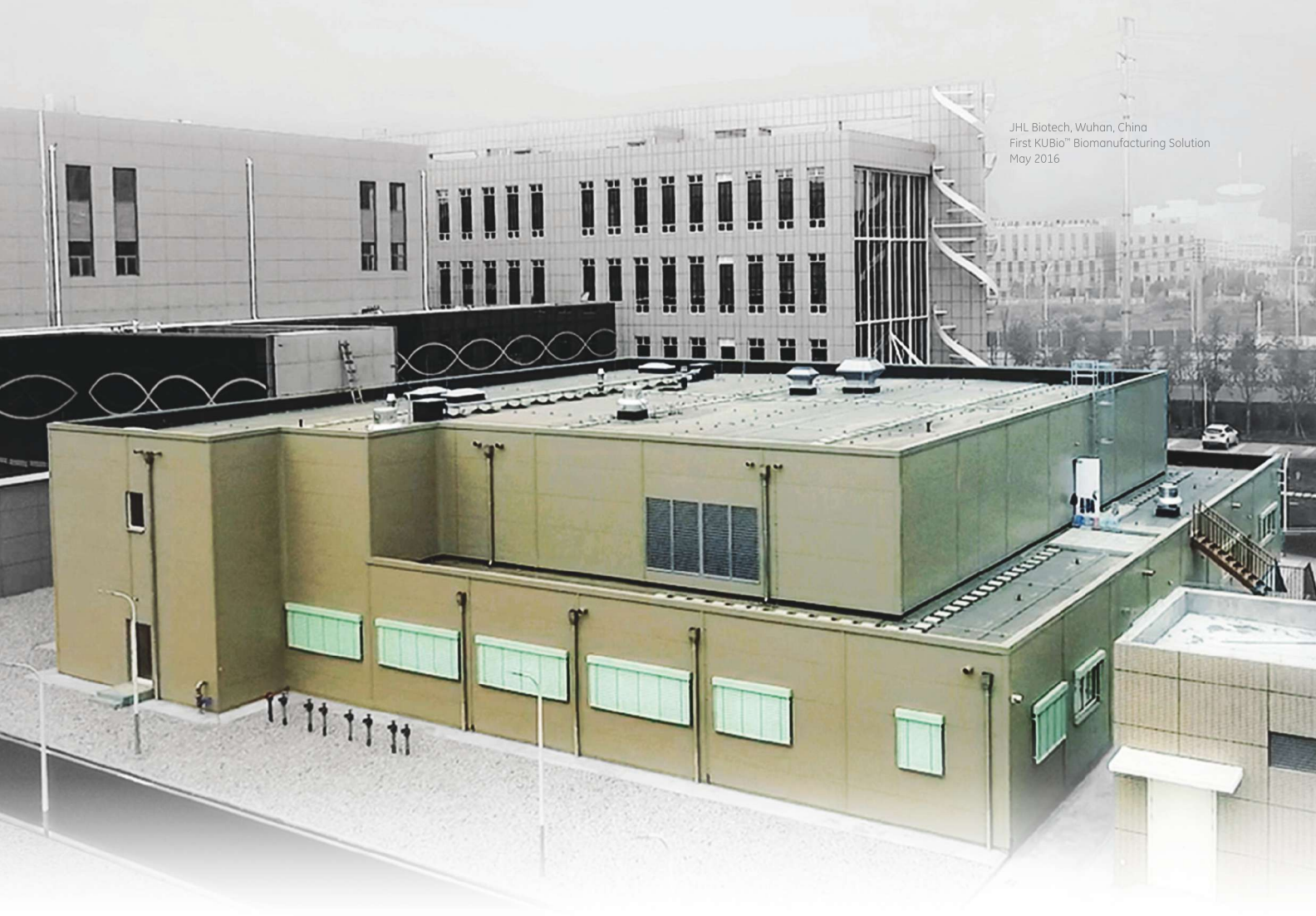

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ASK THE BOARD

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Q How do you answer the question of a centralized or decentralized processing location for personalized medicine purposes?

A IT IS A VALID QUESTION, as the Dendreon example showed that building multiple centralized processing locations may add immediate high-capital investments and raise regulatory questions regarding needle-to-needle logistics. There is no one-size-fits-all answer. New process-facility systems may be used in a centralized mode first, and if required, could be separated and relocated as decentralized systems at a hospital or cancer treatment center processing unit. These systems are becoming more available as prefabricated cleanroom units, which allow the modification from a centralized system to a decentralized system and vice versa. These types of flexibilities are a key requirement for future therapeutic developments and maybe even for rapidly deployable patient-care response systems.

MAIK JORNITZ
is COO of G-CON Manufacturing and founder of BioProcess Resources. He has more than 25 years of experience.

Q What are some key considerations when adopting technologies to enhance clinical trials?

A JUST AS SMARTPHONE APPS have made activities such as personal banking and finding a restaurant seamlessly integrated into people's daily lives, technology in clinical operations can bring the same experience to people participating in clinical trials (e.g., reminders to take the study drug, conduct an assessment). We see data indicating that better, more user-friendly technologies supporting clinical operations positively influence the relationships between stakeholders such as sites and CRAs and sites and sponsors. It is critical to have the end users ready to leverage all the capabilities the technology offers, including involvement early in the design of the technology and change management associated with implementation, as well as with ongoing training and support.

MITCHELL KATZ, PH.D.
has 30 years' experience in the pharma and biotech industries, including preclinical research, pharmaceutical operations, and regulatory affairs. He is the Head of Clinical Research and Drug Safety Operations at Purdue Pharma L.P.

Q Knowing what you know now, what would you not do differently?

A I WAS THE CEO of Pharmacia and Upjohn in 2000 when we had a chance to bid for Knoll. I already knew the sellers (BASF) in Germany from some of my previous connections, and I had visited their offices. I also had an edge since I knew the biotech space well. We bid $5 billion and thought we would get it. Abbott took it for $6.9 billion. And now, Humira is the world's No. 1 pharma product at $15 billion in sales. When Abbott's acquisition was announced, it was seen as a potential $500-million pipeline product. If I were to do it again, I would still not go over $5 billion. Outlier "gushers" only come once in a while.

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

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Ritter Pharmaceuticals

On a mission to develop the first FDA-approved, durable-efficacy therapeutic for lactose intolerance

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Cofounded by its namesake, Andrew Ritter, Ritter Pharmaceuticals is developing a treatment — not merely a symptom reliever — for lactose intolerance, which has plagued Ritter himself since childhood. It is entering Phase 3 development with a "gut-microbiome modifier" targeted at the condition, and it is in preclinical testing exploring microbiome-based treatments for metabolic syndrome, liver disease, cancer, and other gastrointestinal conditions.

WHAT'S AT STAKE

In the gut alone, an unknown number of conditions may respond favorably to microbiome-based treatments. Initially, most of the new microbiome therapies focused on disorders that primarily affect digestion of food in general. Ritter's target and founding purpose is more specific and possibly more common than inflammatory bowel disease or colitis. In fact, more than 1 billion people worldwide and over 40 million in the United States alone live with the condition. It is the inability of the small intestine to metabolize the sugar lactose in dairy products, due to the lack of the metabolizing enzyme, lactase. Lactose intolerance can not only produce embarrassing symptoms such as gas, bloating, cramping, and diarrhea, but also lack of weight gain and growth in early childhood and osteoporosis and hypertension in adults from dairy avoidance. The extreme effects of the condition were painfully evident in the youthful years of Andrew Ritter and his twin brother, who then towered above the sickly Andrew. "My twin brother was heavier and bigger than me at that point because I wasn't getting important nutrients and calcium to grow." No treatment existed for the young Ritter or contemporaries.

Starting in the eighth grade, Ritter contacted leading lactose intolerance experts such as Drs. W. Allan Walker at Harvard Medical School and Dennis Savaiano, a former dean at Purdue University. "With their guidance and support, using myself as the first test subject, in my garage I formulated and developed our first prototype product, Lactagen, a dietary supplement that ultimately treated my own lactose intolerance." Ritter says he has been symptom free taking the supplement consistently. He cofounded his company with his father Ira in 2004 and eventually commercialized Lactagen as an over-the-counter product. Lactagen sold well, but its status as a supplement limited the claims the company could make compared to a prescription drug. Thus, in 2008, Ritter and his team began developing a second-generation, prescription version of its product: a different, novel molecule, galacto-oligosaccharide (GOS), coded RP-G28. To dedicate all resources to RP-G28 development, the company took Lactagen off the market. In October 2016, the company announced the last patient visit in its Phase 2b/3 clinical study of RP-G28 and expects to have the results in the first quarter of 2017.

Through "colonic adaptation," RP-G28 stimulates growth of lactose-metabolizing bacteria in the colon. "We believe this creates a durable treatment whereby you can tolerate dairy products for a long time afterward," says Ritter. "As you consume dairy products, colonic flora feed off the lactose, so in theory you literally maintain tolerance by consuming dairy." Avoiding dairy for a long period thereafter or having some type of gut disruption could lead to a loss of tolerance, but retreatment should restore it, he says.

The company has staked everything on RP-G28 for the time being. It foresees leveraging the compound in other therapeutic areas such as metabolic syndrome, liver disease, and IBD. As Ritter says, "Scientific findings from exploring the microbiome are becoming a game changer in the healthcare industry." Along with the inherent challenge of exploration shared by other companies in the microbiome space, the company's next steps all depend on the forthcoming clinical data.

ANDREW RITTER
Cofounder and CEO

Vital Statistics

16
Employees & Personnel

Headquarters
Los Angeles, CA

Finances

IPO
$20M

Lead Investors
Broadfin, Baker Brothers, Javelin Venture Partners

Other Partners

Aspire Capital Partners and Knoll Capital Management
$5M Offering

Latest Updates

October 2016:
Concluded dosing and last patient visit in Phase 2b/3 clinical trial of RP-G28 for the treatment of lactose intolerance (data readout expected in Q1 2017).

October 2016:
Completed a $5M offering.

June 2016:
Issued Method of Use Patent for RP-G28 for treating symptoms associated with lactose intolerance and improving gastrointestinal health.

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Risks And Rewards Of **Repeal And Replace**

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"Why do you speak ever of hiding and destroying? Why should we not think that the Great Ring has come into our hands to serve us in the very hour of need? ... Let the Ring be your weapon, if it has the power you say. Take it and go forth to victory!"

— Boromir, *The Fellowship of the Ring*

There is a pivotal scene in Tolkien's *Lord of the Rings* trilogy where the Council of Elrond is debating what to do with the Great Ring of power. Boromir suggests using the power of the ring for good but is rightfully admonished by the rest of the council that it is too powerful to wield and must be destroyed in the fiery chasm of Mt. Doom from whence it was forged. The remainder of the great saga tracks Frodo's efforts to journey to Mordor and destroy the ring once and for all so it can never be used for evil.

The Republican sweep in the 2016 elections similarly hands the enormous power of the Center for Medicare and Medicaid Innovation (CMMI) — which can effectively rewrite long-standing Medicare statutes without Congress's input or consent — to the Trump administration. What to do with this power?

Speaker Paul Ryan's healthcare blueprint, "A Better Way," released last summer suggests an immediate repeal of every key Obamacare provision — the taxes (including the $30B pharmaceutical fee), the funding of Medicaid expansion and subsidies for the exchange plans, the expensive regulations, and the Independent Payment Advisory Board. But it curiously suggests waiting until 2020 to abolish CMMI. Why the delay?

There is now chatter among some Republicans that the CMMI power can be used for good purposes, such as reforming Medicare to a more market-based program. However, Republicans would be wise to dismiss those musings and immediately repeal or at least "guardrail" CMMI — substantially limiting the scope and duration of demonstrations — to ensure that Congress's vital role in the care and nurturing of the program can never be outsourced or usurped again. The people's representatives are far more responsive to beneficiaries and other stakeholders than cloistered bureaucrats, regardless of party. Controversial reforms should go through the deliberative legislative process.

Fortunately, President-Elect Trump's selection of Budget Chairman Tom Price (R-GA) as Secretary of Health and Human Services elevates the most prominent and articulate opponent of CMMI to the most important health position in the government.

In a September 2016 op-ed, Price stated, "The broad powers vested in CMMI, and the agency's interpretation of that authority, have the potential to further degrade Congress's lawmaking authority by shifting decision making away from elected officials into the hands of unelected bureaucrats. In addition, CMMI has an automatic appropriation of $10 billion once every 10 years, forever. Consequently, this little agency can spend that money however it chooses — escaping the oversight authority Congress should have through its power of the purse."

Just as important, Price brings a number of key skills and background to the job. He is a former orthopedic surgeon who operated his own practice and intimately understands patient care and how well-meaning regulations can actually stifle innovation and disrupt care. He is a seasoned lawmaker, using his position as a senior member of the Ways and Means Committee and the GOP Doctors Caucus to author numerous healthcare bills that have been enacted, as well as drafting visionary, comprehensive legislation to replace Obamacare.

THE CHALLENGES OF REPLACING OBAMACARE

The first 100 days of the Trump administration will be focused on repealing and replacing Obamacare. Repealing the numerous taxes and funding for the Medicaid expansion and means-tested subsidies for enrollees in exchange plans is relatively straightfor-

ward. It can be accomplished through a parliamentary tactic known as budget reconciliation, which requires a simple majority vote in the Senate. This means if Republicans stick together they do not need to negotiate with Democrats.

But how to handle the more complicated question of replacing Obamacare? Funding can be provided for a refundable tax credit outlined in Ryan's "A Better Way" blueprint through that same reconciliation bill. But repeal of the costly insurance mandates and a raft of other provisions that micromanage nearly every aspect of healthcare delivery must be enacted through regular order – i.e., 60 votes in the Senate. That reality empowers the newly elevated and cagey Democratic Minority Leader Chuck Schumer (D-NY), as Republicans will need eight of his members to join their 52-vote majority in passing any bill out of the Senate.

Republicans will be pressed to demonstrate how those now covered under Obamacare will be provided coverage under their plan once Obamacare is repealed. But how many individuals are actually receiving coverage under Obamacare, and is that coverage reliable under current law, where the insurance exchanges now appear to be imploding?

Analysis by the Heritage Foundation's Edmund Haislmaier and Drew Gonshorowski takes issue with the Department of Health and Human Services' estimate that 20 million people gained coverage under Obamacare. They point out that estimate is based on survey data rather than calculating the actual change in coverage in various markets. Heritage found that 14 million gained coverage in the first years of Obamacare implementation with 11.8 million through Medicaid and 2.4 million through private coverage. Enrollment in the exchange plans was offset by declines in employment-based coverage.

Additionally, many individuals counted as gaining coverage under Obamacare will keep their coverage under any replacement plan. Trump has said he intends to retain the provision allowing 2.3 million young Americans to remain on their parents' insurance. And many of the newly covered Medicaid lives will continue to be covered through the underlying coverage rules that preceded Medicaid expansion. For example, Ohio estimated that 28.9 percent of Medicaid enrollees who gained coverage in 2015 would have been covered under the old criteria. And the Heritage study found that 1.4 million of the newly covered Medicaid lives occurred in states that did NOT expand Medicaid. Publicity of the Medicaid expansion resulted in coverage of already-eligible individuals.

Just as important, a compelling case can be made that Obamacare is presently collapsing of its own accord. Health plans have been exiting the exchanges in record numbers, leaving just a single plan in 960 counties across the country, including just a single plan in the following states: Alaska, Alabama, South Carolina, Oklahoma, and Wyoming. North Carolina and Arizona have only two insurance plans, with one serving most of the counties.

"A compelling case can be made that Obamacare is presently collapsing of its own accord."

Moreover, funding schemes to stabilize the exchange are expiring or being contested in court.

- Risk corridors which shield plans from excessive losses expired December 31, 2016, and plans are unlikely to receive the $8.3 billion in losses for 2014 and 2015 they are now suing to recover, as Congress explicitly prohibited taxpayer funds from being used for risk corridors in those years.
- Reinsurance subsidies to assist plans with expensive enrollees similarly terminate at the end of 2016.
- The cost-sharing subsidies for low-income enrollees were not funded in the statute, determined illegal by a federal court and certain to be rescinded by the incoming Trump administration.

And under current law, effective in 2020, premium subsidies will no longer be tied to health costs but only grow with the consumer price index, leaving individuals to shoulder the difference in higher premiums.

There is an old maxim: You cannot force a company to lose money. And what would compel health insurers that had already been vilified for substantially hiking premiums and cost-sharing while absorbing huge losses to remain in a fundamentally untenable market that was getting worse?

Republican plans to replace Obamacare will actually secure coverage that is eroding in front of people's eyes but without the heavy-handedness that has disrupted the entire insurance market to assist a small slice of the population that is uninsured.

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.

An Insider's View Of Life
Outside The Academic Gilded Cage

JIM CARDELLI, PH.D.

There is a lyric from an old Bob Seger song in which the aging songwriter, lamenting the loss of his youthful prowess once filled with vim and vigor, wonders where the time went ("20 years now; where'd they go; 20 years; I don't know"). For me, 30 years had gone by and I was still a faculty member at a medical school at the end of 2015; I too thought about the passage of time and pondered the future. As a molecular biologist with research experience in oncology and microbiology who had trained over 30 students, published over 130 papers, and given over 1,000 lectures and seminars, I felt I was at a crossroads in my life. I was directing a drug discovery and development program, with a number of pending patents, yet I was acutely and sadly aware that I had not impacted one patient's life or brought one drug to market. Why was this? What stopped me and others from doing this? Upon reflection, I believe there were two main reasons for this impasse.

First, like many universities in the United States, my school did not have the bandwidth or finances to support technology transfer and business development. The budget for Louisiana universities has been slashed over the last 10 years, accounting for most of this problem. Supporting reduced revenue as a national crisis, a recent report from the Brookings Institute states that only 16 percent of university technology transfer offices actually bring in more money than they spend, and this reflects the accomplishments of a handful of universities. Adding to the barriers of commercialization are the many regulatory issues facing faculty wanting to stay in academia and start a biotechnology company. Finally, startup companies require an inordinate amount of time to nurture, and many mid-career faculty are struggling to get (and keep) grant funding, pay their technicians, train students, give lectures, get tenure, and pay their mortgage while raising a family.

The second reason preventing many (myself included) from leaving the academic gilded cage is fear of the unknown. I had a great paying job and was well-respected; I had great colleagues and students, but I knew nothing about the business world. If I left my academic position to start a company, I would have no salary, and I knew the likelihood of a successful startup was small, so surely financial and personal disaster would befall me.

I do not remember the exact time it happened, but I do remember the date — October 18, 2015. As I pondered my retirement and the uncertain future I faced, an entrepreneurial spark engulfed me. I could do this, I reasoned. If I could earn a Ph.D. in molecular biology from a top university, run a successful laboratory for 30 years, direct a successful drug discovery program (with an ROI of 5 to 1), direct the basic and translational research program for our cancer center for 14 years, and deal with endless manuscript and grant rejections, I could retire and start a company.

LEAVING THE GILDED CAGE BEHIND

Thus, Segue Therapeutics LLC was launched in January 2016, followed by a launch of a subsidiary company, SegueTx-Pancreatic Cancer LLC. The former is a drug-discovery platform with an emphasis on repurposed drugs, and the latter is an asset-centric company advancing a combination of repurposed drugs to treat pancreatic cancer. Repurposed drugs now make up 25 percent of the drug revenue market worldwide and include well-known examples such as Viagra and thalidomide. Cost and time to market are reduced, and the overall risk of failure is smaller than for new chemical entities. There are of course hurdles that must be overcome to commercialize repurposed drugs, including IP issues, off-label prescriptions, and generics, but a variety of contract services is now available to guide development of these drugs along the 505(b)2 pathway.

Becoming an entrepreneur has been a truly amazing experience. I have been immersed in a world I knew existed (peering out often from inside the gilded cage), but I did not realize how empowering it could be. I eagerly learned business language as I had learned science as a graduate student. I wrote business plans, generated business models, put together pitch decks, learned what convertible notes were, made connections, and raised seed funding. My company is now funding research at the university drug discovery program I left behind, historically funded via SRAs (sponsored research agreements) from private companies; the circle is complete.

I was very fortunate in the timing of my retirement from the academic setting, since Shreveport, LA is now beginning to develop an entrepreneurial culture. First, the city hosts a competition called the Louisiana Startup Prize, started in 2014. SegueTx-Pancreatic Cancer entered and finished second to a great company from Pittsburgh, PA. In fact, there were over 100 company entrants, and the majority were from outside the state. Second, the Shreveport Entrepreneurial Accelerator Program (EAP) was launched in 2014 and provides services to help create an entrepreneurial ecosystem by analyzing the viability of products and ideas and matching them with informed investors. Third, the building I work in, InterTech 1, houses a collection of finance and business coaches and other entrepreneurs. The excitement is palpable, and I remember why this type of forward-looking, team-building culture is so enriching.

HELPING OTHERS LEAVE THE GILDED CAGE

It is now November 2016 as I compose this article while riding on a train from Shreveport to Chicago (my hometown), a trip that harkens to a time when transportation was more civilized. As I reflect on this journey, I realize that there are many young (and not so young) scientists who, like me, might want to take the road less traveled but sense the barriers that block their entry. I also recognize that there are many universities in Louisiana, and throughout the United States, that have accumulated valuable assets that lie fallow for lack of resources to commercialize them. Over the past few years I've also witnessed graduate students becoming increasingly interested in combining business and science. Unfortunately, most leave North Louisiana for lack of the appropriate business ecosystem, resulting in loss of human assets.

Having gained some acumen in business over this year, I recognized this problem might have a solution. So, we launched Segue Science Management (SSM), a privately-owned Louisiana service-based S-Corp company dedicated to improving economic development in Louisiana through science discovery, education, and commercial development. Our mission is to increase the public's awareness of the importance of science in everyday affairs, while simultaneously facilitating public-to-private technology transfer, thus stimulating the outgrowth of biotechnology companies in the area.

Unlike many younger faculty, I was at a point in my career where I could easily start my companies and devote all my time to their growth. I had many years of experience in program management, a good retirement plan, and support from family. Therefore, the mission of SSM is to assist faculty who want to bridge the gap between academics and business by aiding them in business development. With an increase in biotechnology startups and the entrepreneurial culture that will continue to develop, Shreveport and North Louisiana will foster a new branding and will not simply be thought of as a little city near Texas where there are gambling boats and oil.

Perhaps most rewarding to me over this last year is the story of two of my last students who graduated with a Ph.D. They, like many of their peers, pondered an uncertain future where NIH funding rates remain unacceptably low and faculty positions are difficult to obtain with the glut of postdoctoral fellows. So, Dr. Alana Gray cofounded Segue Science Management and will act as President, and Dr. David Coleman co-founded Segue Science Labs where he will live his dream of running a research laboratory to discover and develop technologies that can be commercialized. As a huge bonus, North Louisiana retains young talent, and new biotechnology companies have started. Thus, a seed has formed that, with nurturing, will continue to grow.

Still, like Mr. Seger, I am amazed at how fast time does pass, but every day I wake up, I look forward to what the next couple of years will bring with regard to economic development and increased biotechnology companies along the I-20 corridor and in North Louisiana. Becoming an entrepreneur was one of the most liberating things I have ever done. I have a purpose-driven life again. So, as a scientist, if you can present an exciting seminar (like pitching in business), write a good manuscript/grant (similar in many ways to writing a business plan), manage a laboratory (it is a small business in many ways), coach people, and so on, you have the tools to start a company and have an impact on health and the economy. So, I encourage science students and faculty of all ages to frequently and intently examine the world outside the gilded cage – outside your comfort zone. You might be surprised to learn that the cage has no lock, and as President Roosevelt famously stated at the start of WWII, "we [you] have nothing to fear but fear itself." L

JIM CARDELLI, PH.D., is CEO and Founder of Segue Therapeutics LLC, an early-stage biotech focused on repurposed drugs.

SUE DILLON, PH.D.
Head of Janssen Immunology

Janssen Immunology

SCIENCE & MARKET DRIVERS

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

From discovery through development, commercial savviness teams up with scientific progress in this J&J business unit.

The name Janssen lives on in the pharmaceutical organizations of Johnson & Johnson, carrying the meaning its founder, Dr. Paul Janssen, gave it through his namesake company's achievements: bold but logical innovation that sometimes goes beyond serving markets to creating them. He taught that vast new markets can emerge in response to products that are the first to address a commonly accepted condition. Yet the contemporary Janssen biopharma entities don't just replicate the DNA of drug discovery and development inherited from Dr. Janssen; they have gone on to explore all emerging pathways to new therapies for a widening variety of disease areas. One of the best examples of the expansion in approaches and areas is Janssen Immunology.

Sue Dillon, Ph.D., who heads the company's global therapeutic area of immunology, updates us on how Janssen Immunology has changed strategically since she last spoke with us for our story on Janssen Biotech in March 2012. She especially focuses on how the company and the immunology group use market insights to guide strategy, therapeutic focus, and product development. In doing so, she also describes Janssen's main mechanism for marrying the precommercial and commercial functions — its unique, multi-unit structure.

"Our organization drives end-to-end drug discovery through late-stage development and integrates the R&D and commercial groups to achieve short-term project execution, as well as longer-term strategic planning," Dillon says.

Structure Power

Immunology is one of five therapeutic areas (TAs) in the Janssen Research & Development organization, along with cardiovascular & metabolism, infectious disease & vaccines, neuroscience, and oncology. The TAs work together with functional units — such as Janssen Biotherapeutics (large molecule expertise), Discovery Sciences (small molecule expertise), Global Regulatory Affairs, and Global Clinical Operations — to execute discovery and development projects. As Dillon observes, immunology is a key growth driver for the company globally, with almost $6 billion in annual sales mostly from four products — Remicade (infliximab), approved for treating Crohn's disease and a host of other inflammatory conditions; Simponi (golimumab), for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis; Simponi Aria (golimumab for infusion) for rheumatoid arthritis; and Stelara (ustekinumab), for psoriasis, psoriatic arthritis, and Crohn's disease. She says immunology is also a chief driver of growth in value "from the pipeline and scientific innovation perspectives."

One significant new addition inside Janssen and the Immunology organization is its Disease Area Strongholds (DASs), groups of Janssen experts in "priority diseases": inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and psoriasis. Each of the other four therapeutic area units has its own set of DASs, based on common criteria. Dillon explains, "A DAS is chartered based on unmet need, compelling science, commercial potential, and where we have

3 Big Hurdles

We asked Sue Dillon, head of Janssen Immunology – "What are the three biggest changes or challenges your group faces for the future?" Dillon answers:

We seek opportunities to achieve the following goals:

- Remain at the forefront of science with the breakneck speed at which R&D and technology are advancing and harness the "explosion" in areas like the microbiome to drive continued innovation.
- Unlock the early triggers and signs of immune diseases to induce tolerance or even intervene before patients develop active disease – move toward prevention, interception, and cure.
- Design development programs to satisfy regulators and payers, empower patients and physicians, and provide postapproval, real-world evidence to substantiate the value any new medicine brings.

achieved or look to achieve the capabilities and pipeline that will deliver transformational medical innovations for patients and leadership for Janssen."

Each DAS consists of an R&D leader, a global commercial coleader, and "a core team of disease area R&D experts in discovery, translational medicine, and development," she says. "The DAS leaders work closely with our discovery and development groups and with the Johnson & Johnson Innovation Centers to scout and access compelling external science and innovations that align with the DAS strategy."

It would take a wall chart to illustrate the entire variety of legal and operational entities now bearing the Janssen name, from Janssen Biotech, the commercial arm of Immunology and Oncology in the United States, to Dr. Paul's heritage company Janssen Pharmaceutica in Belgium. But the therapeutic area units are all global, as are many of the functions that support them, including Janssen Global Services, which contains the Global Commercial Strategy Organization and Communication & Public Affairs.

In recent years, says Dillon, the company has augmented its internal forces with external relationships by creating and building the Johnson & Johnson Innovation group, now with Innovation Centers (ICs) in California, Boston, London, and Asia Pacific, and JLABS incubators in San Diego, San Francisco, Houston, Toronto, and Cambridge, MA. "The ICs are designed to access scientific innovation, working with biotechs and academic leaders, to bring in cutting-edge scientific projects at the discovery and early development stage that are aligned with our scientific strategies," she says. "We typically work collaboratively with partners and retain an option to bring the assets into our portfolio at defined milestones."

The company has added several innovation incubators in recent years: the Janssen Microbiome Institute, led by Dirk Gevers, former group leader at the Broad Institute and researcher on the Human Microbiome Project; the Disease Interception Accelerator, led by Ben Wiegand, a veteran J&J executive; and Janssen Immunosciences, led by Murray McKinnon, another J&J veteran, which is "advancing new immunology concepts with broad therapeutic potential." The groups interact with the TAs and J&J ICs to leverage their capabilities.

Therapeutic Progression

In immunology, a therapeutic area that has chiefly concerned inflammatory and autoimmune diseases, the existing treatments have transformed patients' lives but tied them to a lifetime of drug maintenance. Of course, as with any chronic therapy, drug resistance can grow, and side effects may worsen over time. Thus, the next generation of immunology medicines must meet a higher standard, not just improving on current agents but surpassing them with a limited course of treatment that brings the disease to a halt.

"We are focused on bringing transformational innovations to patients with RA, IBD, and psoriasis where we believe there is still a huge unmet need, even with the medicines we and others have delivered in recent years," Dillon says. "RA and IBD patients rarely achieve full remission, so we are focused on new mechanisms of action that we believe can induce immunologic tolerance, restore homeostasis to the immune system, and/or eliminate pathogenic autoimmune cells in patients with established disease. At the same time, we're building the capabilities to identify and treat these diseases

Paying & Pricing

The thoughts of Janssen Immunology's leader Sue Dillon on the central issues in the drug-pricing controversy shed some light on the company's approach:

We consider three fundamental components when pricing our medicines:

VALUE. We consider the value of our products to patients and to society as a whole, including elements important to governments and other payers, such as clinical benefits and risks versus the standard of care, improvements in the patient experience (better quality of life and higher satisfaction with treatment), and impact on societal and economic factors (total cost of care, disability and productivity, and the benefits to society of reducing caregiver burden).

INCENTIVE FOR INNOVATION. In order to continue to incentivize investors to fund biomedical innovation, we must provide returns in line with their expectations. We support the model that ensures that when our IP protections and regulatory exclusivities end, generics and biosimilars are introduced, generally leading to significant decreases in price.

ACCESS AND AFFORDABILITY. Recognizing that economic and healthcare circumstances differ vastly and that cost can often be a barrier to access, we use a wide variety of approaches, appropriate to the specific reimbursement systems and legal guidelines of various countries, to ensure and sustain broader access to our medicines. Using tools such as tiered pricing and partnerships with public health organizations, we strive to engage stakeholders to help achieve broad and timely access to our medicines in a way that is affordable locally. We are working with payers to explore innovative approaches that tie reimbursement to health outcomes, reflecting the true value our medicines bring to patients and the healthcare system.

We want our drugs to remain broadly accessible by ensuring the net cost is in line with other currently available biologic therapies. We offer a number of patient support programs to ensure broad accessibility, helping support eligible uninsured and underinsured patients to have access to treatment through the Johnson & Johnson Patient Assistance Foundation. In 2015, Janssen helped approximately 762,000 commercially insured patients to significantly reduce out-of-pocket spend for its medications.

In 2015, Janssen donated medicines and funding to enable the Foundation to provide medicines to approximately 100,000 U.S. patients without adequate financial resources and prescription coverage.

much earlier to intercept or even prevent the destructive disease processes."

All current treatments for such conditions suppress key proteins in the pro-inflammatory pathways, including TNF (tumor necrosis factor), JAK (janus kinase), IL-23, IL-17, and various cytokines, mainly to moderate symptoms. But as science produces more and more knowledge about the root causes of those diseases, hope grows for something more like a cure. "Better understanding of genetic susceptibilities and environmental factors including the host microbiome is setting us up for defining the antigenic triggers of autoimmune disease, which could translate into therapeutics that can target the auto-reactive cells that escape from the normal mechanisms that keep those cells inactive," says Dillon. The same knowledge would make it possible to identify patients earlier in the disease cycle, treat them sooner, and potentially induce long-term remissions and cures, in her view.

"That is where the science is leading us. Because of the breakthroughs in genomics and the emergence of various platforms that allow us to sequence and understand the T-cell receptor repertoire, we can learn exactly what antigens are recognized by T cells in people with autoimmune disease and how autoreactive clones differ in populations at different time points in the disease, and so on," she says.

> "We typically work collaboratively with partners and retain an option to bring the assets into our portfolio at defined milestones."

Janssen is working on "shifting the paradigm" from blocking inflammation to not only interrupting the disease triggers but also reestablishing "immune homeostasis," according to Dillon. "We want to restore the normal constituents and mechanisms that should be there as part of normal immunosurveillance in order to block autoimmune responses."

In the near term, however, research will still concentrate on creating "better and better cytokine blockade," she says. She cites the example of advanced therapeutics for psoriasis, which began with Enbrel (etanercept), moved to Humira (adalimumab), then to Stelara (ustekinumab). "As we showed in a head-to-head study years ago, Stelara is superior to Enbrel. Now with the IL-17 and IL-23 blockers, both clearly are the most potent mechanisms out there."

Janssen recently presented findings from a Phase 3 trial with its IL-23 specific antibody drug candidate, guselkumab, in patients with moderate to severe plaque psoriasis, and showed the superiority of guselkumab over Humira. Additional data from a large Phase 3 development program, which includes a second trial comparing guselkumab with Humira and a third looking at patients who have an inadequate response to Stelara and are treated with guselkumab, are forthcoming. Guselkumab has been submitted to the FDA and EMA for approval. Dillon makes the point that the very design of the trial shows how much higher the bar has risen as newer drugs have entered the market. Janssen is also pursuing other indications for its newer therapeutics. As with Stelara, which has now been approved for Crohn's disease in the United States and European Union, the company is eyeing plans for guselkumab in Crohn's disease and other lifecyle indications such as psoriatic arthritis.

"None of the existing drugs for Crohn's, RA, or IBD interrupts the process," she says. "They dampen inflammation and achieve remarkable effects in symptoms and remission in some cases. But in general, if you stop the drug, the disease remains, and, particularly in RA and IBD, many patients who initially have very good response lose their response for a variety of reasons, and there has been a large surge in TNF-inadequate responders in Crohn's disease, for example. Therefore, we believe Stelara will have a large impact in such cases."

In addition to RA, IBD, and psoriasis, the group has launched early efforts with Stelara and Simponi in other autoimmune diseases, including Lupus and Type I Diabetes (T1D), looking at how they may restore tolerance in the immune system. In a collaboration with the Lupus Research Alliance, it is evaluating Stelara in a Phase 2 study, and it recently launched a proof-of-concept study with Simponi in patients with newly diagnosed T1D.

Immunology is also exploring the potential role of the microbiome as a predictor of inflammatory and autoimmune disease, aiming to develop related therapeutics and diagnostics. In establishing the Janssen Human Microbiome Institute and the Disease Interception Accelerator, the company is greatly expanding its therapeutic targets and approaches, according to Dillon. Some of the new targets are T1D, gestational diabetes, COPD, perinatal depression, presbyopia and cataracts, and oropharyngeal/cervical cancer.

"These are not traditional drug discovery or development efforts," she says. "These incubators are looking at the diseases in a very different way. They have selected the diseases very carefully, based on the latest knowledge of risk factors and access to patients at high risk of developing certain diseases, and they will be figuring out approaches we can use to intervene." Unlike the incubators serving the entire Janssen group, Janssen Immunosciences is a dedicated part of Dillon's team but is focused more on immunology science, looking for platforms that could be applicable in many different diseases, even outside of the autoimmune area.

So, by this time, you're wondering how the commercial input enters this picture of disease and therapeutic mechanisms. Well, the first common denominator of mechanisms in development and markets in motion is the future. Janssen Immunology is not poring over new treatment modes just for its amusement; its scientific aims are directly tied to the practice settings, treatment paradigms, and cost structures of real-world healthcare systems in which its products will compete — otherwise known as "the market." Perhaps the potential benefits for those systems should be obvious, but in fact they must be proven, expressed, and communicated to the market players, from patients to physicians to payers. What is the "value proposition" of stepping beyond treating symptoms to halting disease?

Commercial Integration

In healthcare, market needs and medical needs are not identical, but they are closely related. If a company can introduce products that, say, liberate patients from chronic disease and payers from the related costs, of course it has a potential competitive advantage. But to accomplish such a feat takes effective communication in two directions — from the market to the science and from the science to the market. Janssen Immunology relies on a key ally in the company, the Global Commercial Strategy Organization (GCSO), to ensure that communication.

As Dillon explains, the GCSO furnishes expertise in strategic analytics, market research, market dynamics, modeling, commercialization, strategic marketing, market access, medical affairs, and other related intelligence to establish the strongest possible product profiles for treatments in its current portfolio, as well as therapeutics advancing through the pipeline. "Our unique DAS model promotes close collaboration between the GCSO aligned to disease areas working strategically with their R&D counterparts. This ensures that insights from KOLs and experts in the field gathered by the GCSO team are communicated to scientists in the lab to bring about the next wave of transformations for patients," says Dillon.

Each DAS team has both an R&D leader and a global commercial strategy leader to ensure dual, end-to-end oversight for the portfolio. "The DASs are well connected and work closely with discovery, translational medicine, and late-clinical development teams," she says.

Dillon says the role of the GCSO is critical in promoting alignment among the various regions on global positioning, as well as adoption of best practices from around the world. "As a global organization, it is important that we remain in tune with the needs of a diverse marketplace across North and Latin America, EMEA, and Asia Pacific. The GCSO facilitates regional collaboration and makes sure our approaches to development, marketing, medical affairs, and other activities are tailored accordingly to extend the reach of our medicines to patient populations on a global scale."

A critical component of the R&D-commercial interchange is addressing the needs and demands of the payer constituency. "Increasingly, market access can represent a major challenge for new and existing projects, and ensuring our development plans are well aligned to the future needs of all stakeholders, including payers and reimbursement authorities, will help ensure that patients receive the treatments that they need." When important for the gatekeepers, comparison trials that prove a product's superior benefits and cost-advantages are one example of development reflecting commercial input.

Once a product achieves approval and enters the market, the GCSO takes the lead, but the TA team plays on. "The GCSO maintains an active role throughout the lifecycle of a product, and its people serve as coordina-

Immunology Into IO And New Territories

Perhaps the strongest siren call for a wider therapeutic focus by Janssen Immunology would be in immuno-oncology (IO), where Janssen appears to lag behind other large companies. Head of Janssen Immunology, Sue Dillon, gives the following explanation of how her group will contribute to the company's crossover into IO, as well as other new therapeutic areas.

Immuno-oncology is among the most active areas of R&D investment at Janssen, with 15 immuno-oncology compounds currently in our pipeline. Our IO work is being led by my counterpart, Peter Lebowitz, M.D., Ph.D., who heads up the Janssen Oncology TA (therapeutic area). Realizing that the majority of patients are not responding to currently approved IO agents, his team is pursuing novel approaches or modalities. The result is a pipeline that is highly competitive across the industry. We believe we will expand the impact of immuno-oncology by focusing on the next wave of new, innovative modalities.

Because of our expertise, we look at immunology holistically. Indeed, the targets for the checkpoint inhibitors are on our radar screen as potential targets for autoimmune disease, with the idea of blocking costimulatory targets or creating agonists for co-inhibitory receptors to dampen T cell activation (i.e., the opposite of oncology). We are also working across the TAs to better understand the opportunity of immunological underpinnings in a multitude of diseases, including treatment-resistant depression, for example.

To further explore the role of innate and adaptive immunity in multiple diseases, we've recently formed a group called Janssen Immunosciences, which aims to bring immunology expertise and capabilities across the TAs. This is led by Murray McKinnon, who also currently heads Immunology Discovery. Together with his colleague Anish Suri, who is based in Beerse, Belgium, he has established the Immune Repertoire Center where they are mapping the immune repertoire for disease monitoring, interception, and immunomodulation of T-cell mediated diseases.

Toward A More Perfect Diagnosis

Drug/device combinations have been a key focus of Janssen and Janssen Immunology, headed by Sue Dillon, who describes how the coordination of drug and diagnostic development has progressed in her group in recent years.

We continue to make progress in the area of drug and diagnostic development by incorporating biomarkers that may predict drug response or aid in segmenting patient subpopulations into many of our clinical-trial designs. We are also exploring digital health applications for clinical trials and to further enhance drug products. For example, RA-RA, or remote assessment in RA (rheumatoid arthritis), is a new digital biomarker program implemented by Janssen that uses wearable, commercially available activity monitors and a smartphone mobile app aligned with the cloud to study the daily fluctuations in disease for patients with active RA. This program represents one of our many initiatives to integrate digital technology into our work. Overall, our strategic biomarker discovery work and our digital health applications aim to understand unmet needs at the molecular, cellular, and patient level, trying to predict responses and create more personalized treatment programs.

tors across the regions and as facilitators of several postmarketing registries evaluating safety and clinical outcomes for patients receiving our products."

For example, through the medical affairs team, immunology maintains PSOLAR (Psoriasis Longitudinal Assessment and Registry), a prospective, disease-based observational study assessing patients with psoriasis who are receiving or are candidates for treatment with systemic therapies. A key component of the company's regulatory commitment to conduct postmarketing safety monitoring for Stelara and infliximab, PSOLAR is fully enrolled with more than 12,000 patients to be followed for up to eight years. The key demographics, disease characteristics, and medication history of patients were collected at enrollment. Adverse events and efficacy data are collected longitudinally. A PSOLAR global steering committee manages epidemiological research on psoriasis and its therapies.

Postmarketing research and other commercially important input not only inform product positioning on the market but also feed back into the scientific end of drug discovery and development. "By design, it all starts within a disease area, where we see the key unmet medical need based on disease understanding and deep market insight, which drive our selection of a target, as well as the means of administering the drug and the other attributes such as biomarkers." (See "Toward a More Perfect Diagnosis.") But the scope of market modeling for a product points toward the future, she says.

"We need to think about the time horizon. When a drug comes to market, what will the field look like, and how may the unmet medical need change by that point? As we go down the path further in development, we keep refining the target profile."

Facing Biosimilar Competition

At the time of our conversation, Dillon has just come from a "town hall meeting" of the Janssen Immunology team at its R&D hub in Spring House, PA, including the virtual presence of its people in La Jolla, CA; Beerse, Belgium; and other sites around the world. Such periodic gatherings serve to update the team on current developments, internal and external, that affect the organization and its efforts. At this meeting, the progress of the pipeline portfolio was discussed, as well as a more perturbing topic — the federal court decision in Boston that ruled a key patent for Remicade invalid, paving the way for a biosimilar version of the product by Pfizer. Aside from the unusual spectacle of two pharma giants locking horns over one's intent to produce a knockoff, the decision was significant for forcing Janssen to face biosimilar competition, obviously much earlier than it wished.

"Of course, we are not in agreement with the decision, but at the same time, we've known that biosimilars are coming at some point, and we've been well prepared for that for years," Dillon says. "We support the regulatory framework for the approval of biosimilars as long as the standards and policies are based on sound science, with the understanding of the complexities of biologics."

But the overarching theme of the meeting extended the awareness of competition and adversity in the market even further. "We are trying to get people's heads around how the future of healthcare may develop and affect us," she says. "This is a recurrent theme in the conversations with our group — science is evolving at an unprecedented pace in general and in immunology, and at the same time, the whole ecosystem of healthcare is rapidly changing. We need to remain focused on being medical innovators and driving innovation. That is critical in R&D but just as much in the commercial space. The competitive nature of the market drives the science and our business forward."

Dillon's words somehow invoke a mental picture of the Janssen model, as displayed by Janssen Immunology. Perhaps the idea of keeping its groups relatively small and specialized inside the giant protective dome of a corporation has traction. Smaller groups, say the size of Dr. Paul's original Janssen, tend to think boldly and urgently; big companies can have a longer-term vision, if they are also brave enough to use it. L

INSIDE

TAKEDA ONCOLOGY'S PATIENT ADVOCACY PROGRAM

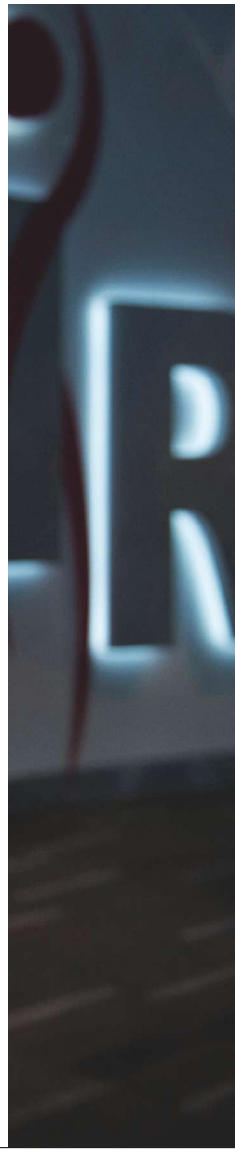
ROB WRIGHT Chief Editor @RfwrightLSL

LIZ LEWIS
Head of Patient Advocacy
Takeda Oncology

So how does a lawyer become head of patient advocacy at one of the largest biopharma companies in the world? In Liz Lewis's case, it started at the Washington, DC-based law firm, Epstein, Becker and Green where she represented healthcare and life sciences companies and served as cochair for the firm's pharmaceutical practice group. In 2002 she left the firm to join Takeda where she is currently chief counsel and head of patient advocacy at Takeda Oncology. Although her primary responsibility is setting Takeda Oncology's global legal strategy, in her patient advocacy role she works closely with cancer patient advocates to support access to oncology therapies. Lewis sat down with me to share how she helped enhance Takeda Oncology's patient advocacy organization.

A "Listening Tour"

"When I came into this role I didn't have to build the patient advocacy program from scratch; we had a long history dating back to when we launched our first product, VELCADE [bortezomib], in 2003," Lewis shares. VELCADE is primarily used to treat people with multiple myeloma (a cancer of the plasma cells). But due to treatment innovations over the years, the myeloma patient experience had dramatically changed (i.e., patients living longer). So, Lewis decided to enhance the existing patient advocacy program, starting by conducting an environmental assessment.



She refers to this as her "listening tour," which required a two-pronged approach — internal and external. Internally, she looked at what the company's priorities were versus the needs of patients, as well as the company's existing footprint. As Takeda Oncology had evolved into a global operation, she wanted first to understand what going "global" meant for patient advocacy. She also compared how the patient advocacy function had traditionally engaged with the rest of the company and how that may (or may not) have been evolving. "We quickly identified that patient advocacy was playing an active role in the R&D organization, particularly around clinical development," Lewis states. "Recently, we announced the launch of the INSIGHT-MM study, which will be the largest pharmaceutical company-sponsored study of its kind in multiple myeloma, with the goal of enrolling a minimum of 5,000 patients 18 years or older with newly diagnosed or relapsed/refractory multiple myeloma globally. The steering committee for this project included one of Takeda's patient ambassadors, who also happened to be a physician."

To begin internal dialogue, Lewis admits to employing a communications template. "I wanted the conversation to be very consistent from one person to the next so we could understand the insights we were hearing," she explains. When conducting her listening tour, Lewis shared with people (in advance) the purpose of the conversation, but not the template itself. "I felt it was very important to try to capture first impressions," she confides. "If they had the template in advance, it had the potential to bias some responses." Some of the categories of the template included:

- ENGAGEMENT i.e., How do people currently engage with patient advocacy?
- EXPERIENCE i.e., Based on their function, what has been their experience either at Takeda or a previous organization?
- VISION i.e., What role should patient advocacy play at Takeda?
- EXPECTATIONS i.e., Is advocacy meeting their expectations?
- OPPORTUNITY i.e., Where could advocacy play a larger role?

When it came to utilizing the listening tour to enhance Takeda Oncology's patient advocacy organization, Lewis began that process by meeting with a lot of internal groups like medical affairs, market access, sales, corporate communications, and clinical and their leaders to understand how they have engaged with Takeda's advocacy unit. "We sought first to understand if Takeda's patient advocacy was meeting their needs, and if there was more we should do," she explains. Because the myeloma patient experience had changed so much, one of the first things Lewis's advocacy organization did was conduct a patient "journey" mapping exercise. "We wanted to make sure we understood what the current patient experience was and how we could potentially support and advocate for patients within our company," she says.

"Then we looked at the activities we had traditionally done as an advocacy organization and assessed those activities to determine whether we were doing was truly supporting the patients." The team also met with external advocacy organizations Takeda had worked with in the past, as well as some in oncology with whom they had not previously worked. The goal of these meetings and the format of the discussions were similar to the internal conversations: to understand from these organizations what their experience working with Takeda Oncology had been, whether the group was meeting their expectations, and to uncover any potential opportunities.

Completing the listening tour took a few months. Some of the deliverables of these meetings included a revised advocacy organization structure and new vision and mission statements that reflected the global positioning of this function. "We didn't want just a new advocacy platform," Lewis states. "We wanted to better educate the organization on the overall advocacy function and how best to support patients." The new structure was pressure tested before implementation by meeting regularly with those involved in the listening tour. "These meetings were a great barometer to assess the impact," she says.

Getting Close To Patients

Of course, interacting with patients in the biopharmaceutical industry has always been limited due to regulations and the use of intermediaries (e.g., physicians and nurses) to share product information. "To try to bridge the gap between company and patients, Takeda created a 12-member Patient Leadership Council (PLC) to gain input from patients to help our decisions reflect their

needs and expectations and to include clinical trial design and patient education resources. "In 2002, we started working closely with advocacy organizations," she explains. "We learned there was a lack of information about what multiple myeloma was, and patients struggled to have informed discussions with physicians about their disease." As a result, Takeda Oncology developed an ambassador program (see section titled "Patient Ambassadors") where patients were engaged to educate other patients about the disease. During the development and implementation of the ambassador program, the company recognized that some patients were much more engaged in the myeloma patient community than others. "Some patients, not necessarily ambassadors, were actually blogging about their disease," she explains. "Others held strong and valuable opinions about how to improve our clinical trial programs." In other words, the company discovered that there were patients with much to contribute beyond that of the role of ambassador. So, the company created the PLC, which comes with a year commitment from each member.

"For the PLC we look for patients who are leaders in the multiple myeloma community and engaged in advocacy, education, and empowerment of patients who could provide meaningful insights," she states. "For example, in this group we have a patient who's a former physician. We have another patient who has significant expertise in government policy and access. Another member is a former teacher who is really driven to help educate others." Lewis shares that some of these patients came to Takeda's attention as a result of their desire to share their personal multiple myeloma journey with other patients. Others were identified by their treating physician. "If we are looking to get input from patients on how to improve clinical trial protocols, for example, we are looking for a patient with a certain type of experience," she clarifies. "Having someone on the PLC who has a medical background or actually participated in a clinical trial is someone with significant knowledge that can help us."

In addition to its focus on patients, Takeda Oncology also concentrated on building and delivering a global advocacy expertise internally. "We created a global oncology patient advocacy council [GPAC]," she continues. That group has about 15 Takeda employees working together to help not only build the infrastructure to better execute a global oncology patient advocacy presence but also to gain alignment between internal and external stakeholders (e.g., patient advocacy organizations). "Internally we talk about what the objectives are for oncology patient advocacy from a global perspective," she elaborates. "The really interesting thing about patient advocacy is that once you step outside the United States, every place seems to think about it a little differently." While Lewis says there are laws and regulations that shape how a company's patient advocacy organization should act, for Takeda (within the United States at

Patient Advocacy: More Than A Survey

Before Liz Lewis, chief counsel and head of patient advocacy at Takeda Oncology, joined the company in 2002, the organization was already well engaged in patient advocacy. "When I walked into the legacy Millennium pharmaceuticals organization, I was the lawyer in charge of helping to build a legal function that could serve our commercial organization," she explains. "We were just launching our first oncology drug, VELCADE, so there were a lot of questions around how to engage with patients."

At the time, patient advocacy within biopharma was an emerging function. Lewis had to determine how to play in a space where there really weren't any defined rules yet, but there was most certainly significant scrutiny. "Putting patients first means listening to them in order to understand their concerns, priorities, and needs, and then weaving that insight into the drug development and commercialization processes," she says. For example, not long ago Lewis received an unsolicited email from a patient who had worked with the company on an adherence program. At the end of the program, the patient was asked to complete a survey. In the email, the patient explained that a lot of companies ask him to complete surveys. "But he said what we did differently was, after he submitted the survey, we actually sat down with him and asked a lot of in-depth follow-up questions. He said, 'You really thought about my answers and cared about what I thought,'" recalls Lewis. "That's why we decided that to truly understand a patient's journey we had to do more than just conduct a survey."

Want to understand how to better design a clinical trial? Don't bring in patients just to give advice on protocols. "While protocols need to achieve meaningful clinical and scientific endpoints, trials also need to be designed so they aren't too onerous for the patient," she states. A simple, yet profound question Lewis says to consider when designing a trial is, "Does what we are asking make sense for the patient?"

Don't Burden Patients With Advocacy Work

At Takeda Oncology, the company has a number of components to its patient advocacy initiative. For example, it employs patient ambassadors, folks with multiple myeloma who go out and speak to other patients on behalf of the company. Takeda also has a global patient advisory council (GPAC) consisting of employees throughout Takeda's global organization, and a patient leadership council (PLC) consisting of multiple myeloma patients who advise Takeda on its patient engagement efforts. "It is important to remember that we are working with a patient population that has cancer," says Liz Lewis, chief counsel and head of patient advocacy at Takeda Oncology. "We certainly don't want their work with us to ever become a burden."

In other words, developing an effective patient advocacy program requires flexibility. "We aim for a mix of live meetings, calls, and then, in some circumstances, one-on-one conversations if something comes up," she shares. "We have frequent touches with our PLC members, at least quarterly, where we might be doing a group call. Once a year we do try to get everybody together." Lewis believes that once you develop rapport in working with a group of external patient advocates, having in-person meetings becomes less important. "We find we're actually able to quite effectively connect via conference calls," she concludes.

least), GPAC has been helpful in shaping how the company should think (i.e., incorporating cultural norms).

According to Lewis, getting patients involved in Takeda's patient advocacy efforts really goes back to developing a relationship geared toward understanding their interests and skillsets, as well as what they are willing and able to commit to. "And all of that has to be done within the constraints of working in a highly regulated environment," she asserts. "When a patient initiates contact with us, it becomes a priority to understand what they have to say and identify any opportunities for future engagement."

Patient Ambassadors

One of the most important components of Takeda Oncology's patient advocacy initiative is its patient ambassadors, of whom the company currently has about 30. Ambassadors speak at educational seminars and medical meetings, patient events, and to patient support groups about their experience to create awareness of multiple myeloma. Every year the company conducts multiple live, unbranded educational programs, many of which involve patient ambassadors sharing their stories.

Ambassadors are compensated for their time and travel expenses, something Lewis believes important to making such an initiative successful. "Your group of advisors or speakers should be a well-rounded representation of patients," she explains. "If you don't compensate people fairly who might have to take time away from their jobs to conduct a program, then your initiative may include only the more affluent who can afford to serve." According to Lewis, in many of Takeda Oncology's programs the company is looking for patients not only to help educate other patients but also advocate on those patients' behalf, while also providing the company with honest feedback on how to continuously improve.

Because ambassadors are speaking as representatives of the company, the materials have to be developed and approved in a very specific manner. "When a patient is delivering a program, they are not sales reps or physicians," Lewis reminds. "Their job is not to convince other patients to take the product or to talk about product benefits. Their job is to talk about their personal, non-medication-related experience and maybe some other challenges [e.g., getting to the clinic]."

That said, because they are speaking on behalf of the company, Lewis employs an agreement very similar to what is used to manage Takeda's physician speaker bureau. "We engage our patient ambassadors a little differently than we do our leadership council," she explains. "We like to have our ambassadors under an agreement for a pre-specified period of time." Takeda also closely monitors ambassador speaker programs to ensure they are meeting company standards for quality. This proves useful when deciding whether to renew an ambassador agreement when it comes due. "The environment changes all the time," Lewis reminds. "For example, we just brought a new drug to market. So we need to continuously think about what our needs are balanced against the needs of the patient to adequately determine what the size of the ambassador bureau should be." As for what Lewis looks for in ambassadors, it's not only having a strong desire to educate but also finding those patients who possess strong public speaking skills. "We want people who are comfortable enough to be able to share their story publically and committed to doing it in an appropriate manner that is consistent with our highly regulated industry," she explains.

Lewis adds that these kinds of patient advocacy initiatives don't happen overnight. "It really begins with listening to patients and getting a perspective that may be different from that of investigators or physicians with whom they speak," she counsels. "But by actively engaging with myeloma patients, you will be able to develop programs that give you an opportunity to create meaningful education for patients." L

Why Pet Health Is The Focus Of A New Biotech Sector

CATHY YARBROUGH Contributing Writer @sciencematter

For Aratana Therapeutics, 2016 was a banner year. The biotech company, founded in 2010, achieved FDA approvals for three of its 10 pipeline drugs. Last year the Kansas City-based company also forged a global partnership with the pharmaceutical giant Eli Lilly, a track record that any young biotech company would like to achieve.

But Aratana is not a typical biotech company. It is one of several companies launched during the past decade to develop cutting-edge small molecule and biologic drugs for dogs and cats with cancer, osteoarthritis, and the other chronic disorders that afflict pets as they age. These new companies are part of a $24 billion animal health industry, which is dominated by Zoetis and several other large multinational companies that produce vaccines, parasiticides, and other products for livestock as well as companion animals. But a very small part of these companies' business is focused on the medical needs of pets with serious diseases.

"Historically, animal health companies have not developed pet-specific medicines," says Steven St. Peter, M.D., cofounder and CEO of Aratana and who was a life science venture capitalist for 15 years at MPM Capital before founding Aratana. "About 90 percent of pet medicines are drugs for humans that veterinarians use off-label in dogs and cats." There are exceptions, of course, such as Merial's melanoma vaccine to treat dogs with stages II and III oral canine melanoma and Zoetis' drug to combat mast cell tumors in dogs.

Pet biotech companies can operate at a faster pace than human-focused biotechs, because they can skip preclinical studies with laboratory animals and go directly to the dogs or cats that are the target species of the drug under development. "We can move from drug lead identification to safety testing and preliminary efficacy studies in about 18 months," says Mark Heffernan, Ph.D., CEO of pet therapeutics biotech Nexvet, headquartered in Ireland. In addition, regulatory requirements, while stringent, are less complex and time-consuming in clinical trials for companion animals than for human patients. (While the USDA oversees animal vaccines and biologics that act through the immune system, the FDA reviews applications for small molecules and other drugs for animals.)

> *"About 90 percent of pet medicines are drugs for humans that veterinarians use off-label in dogs and cats."*
>
> **STEVEN ST. PETER, M.D.**
> Cofounder and CEO, Aratana

ONE HEALTH PROMOTES COLLABORATION BETWEEN ANIMAL AND HUMAN HEALTH COMPANIES

One Health advocates propose that during the preclinical phase of drug development, biopharmaceutical companies consider whether their experimental compounds for human patients also might benefit pet dogs and cats with the diseases targeted by the compounds. "For many years, dogs have been used in preclinical tests to develop human medicines, but the companies did not ask whether the dog also could have benefitted from the drug," says Steven St. Peter, M.D., cofounder and CEO of Aratana.

Pet biotech companies stand ready to collaborate with biopharmaceutical companies in drug development. "We believe it's important for animal health and human pharmaceutical companies to make strategic partnerships and advance science for multiple species at once. The idea of a conscious and very deliberative collaboration has the potential to bring therapeutics to dogs and cats much more quickly," St. Peter says.

Nexvet has launched a subsidiary, Tevxen, to foster its collaboration with human-focused biopharmaceutical companies in the development of mABs that bind with specific therapeutic targets. Using Nexvet's proprietary PETization technology, Tevxen will create two versions of an experimental mAb, one that the biopharmaceutical company will evaluate for human patients and the other for Nexvet to test in dogs or cats. The results of the pet studies could be complementary to a safety or efficacy data package for the human version of the same mABs, says Mark Heffernan, Ph.D., CEO of Nexvet.

A RISE IN CAPITAL-RAISING OPPORTUNITIES

Aratana, the first pet therapeutics biotech company in the U.S. to go public, is also the first one to achieve U.S. regulatory approval for its drugs. Indeed, the company has generated a lot of coverage in the online financial press, especially after it acquired two other pet biotech startups, Vet Therapeutics and Okapi, which respectively specialized in developing antibodies and antiviral drugs.

But in general, biotech companies such as Aratana have been generating a lot of media buzz mainly due to the huge potential of the animal health market. Consider that a 2015 Harris Poll indicated that 65 percent of U.S. households have at least one dog or cat, and 95 percent of U.S. dog and cat owners consider their pets as members of the family. "Over the past 30 to 40 years, pets have become much more part of the family," says Tammie Wahaus, CEO, Elias Animal Health, a spin-off of Kansas-based privately held TVAX Biomedical. "Veterinarians and pet owners are asking for better therapeutics to treat the serious diseases of pets," she adds.

Zoetis' $2.2 billion IPO in 2013 has been credited for alerting investors about the financial potential of the animal health industry. "The IPO spurred investor interest and helped create an ecosystem for smaller companies to raise capital," says Heffernan. In fact, when TVAX launched Elias Animal Health in 2014, it obtained $2 million from investors, even though the initial fundraising goal was $700,000. Aratana raised $40 million in its landmark 2013 IPO. Later that year, California-based Kindred Biosciences' IPO generated over $60 million. Colorado-based VetDC has received more than $8 million from investors since the Colorado State University spin-off opened its doors in 2010. Nexvet, which develops mAbs for pets, has raised more than $80 million from investors since it was established in 2011.

A substantial portion of pet-biotech funding goes toward the costs associated with clinical trials. Aratana's FDA-approved appetite stimulant Entyce was evaluated in a double-masked, randomized, placebo-controlled study that included 244 dogs with various medical conditions. VetDC's multiple clinical trials of its canine lymphoma drug, Tanovea, included 350 dogs at 18 U.S. veterinary centers. Nexvet's placebo-controlled, randomized, double-blind study of its lead compound ranevetmab enrolled 262 dogs at 12 veterinary clinics in the U.S. and Europe.

PARTNERING WITH HUMAN-FOCUSED BIOPHARMAS

Most pet biotechs develop compounds based on human medicines that the companies have licensed from human-focused biopharmaceutical companies. For example, most Nexvet portfolio drugs are based on validated off-patent mAbs that biopharmaceutical companies have clinically tested in human patients. Using its proprietary technology platform, PETization, Nexvet can translate human or mouse mAbs to be recognized as not foreign by the pet species for which the drug is being developed.

By adapting drugs under development or already FDA-approved for human patients, pet biotech companies minimize their clinical risk and development cost. Aratana's Entyce and Galliprant, approved by the FDA for the treatment of dogs with osteoarthritis pain and inflammation, were licensed from RaQualia Pharma, a Pfizer spin-off headquartered in Japan. At RaQualia, Entyce is under clinical development for human patients. Aratana's third FDA-approved drug Nocita, a local postoperative analgesic for cranial cruciate ligament surgery in dogs, is based on Exparel, which the pet biotech licensed from New Jersey-based

> *"Veterinarians and pet owners are asking for better therapeutics to treat the serious diseases of pets."*
>
> **TAMMIE WAHAUS**
> CEO, Elias Animal Health

Pacira Pharmaceuticals. Exparel is FDA-approved for postsurgical analgesia in human patients. In October 2016, Aratana began marketing Nocita to veterinarians. Aratana obtained the veterinary rights to the drug in return for a one-time payment of $1 million to Pacira, which will receive a double-digit royalty payment on net sales.

Galliprant is the focus of Aratana's partnership with Eli Lilly, whose animal health division, Elanco, will copromote the drug with Aratana in the U.S. and commercialize the product outside the U.S. In addition to receiving $45 million up front from Eli Lilly, Aratana will obtain milestone payments and royalties based on Galliprant's sales outside the U.S. In 2014, Nexvet signed a similar commercial agreement for its lead compound ranevetmab with the global animal health company Virbac, headquartered in France. Once regulatory approval of ranevetmab is achieved, Virbac will distribute and market the Nexvet drug outside North America.

FOCUSING ON SHELVED HUMAN ASSETS

St. Peter identifies potential compounds for Aratana to license through his and his colleagues' contacts in the human-focused biopharmaceutical industry and by networking at scientific conferences. At VetDC, Steven Roy, president and CEO, targets the companies conducting preclinical research at CSU's College of Veterinary Medicine and Biological Sciences. "Very few, if any, of these companies are interested or have the strategic bandwidth to develop their compounds for companion animals," says Roy. Like the other pet biotech companies that license drugs, VetDC enables biopharmaceutical companies to leverage their considerable investment in R&D to benefit companion animals and potentially their bottom lines.

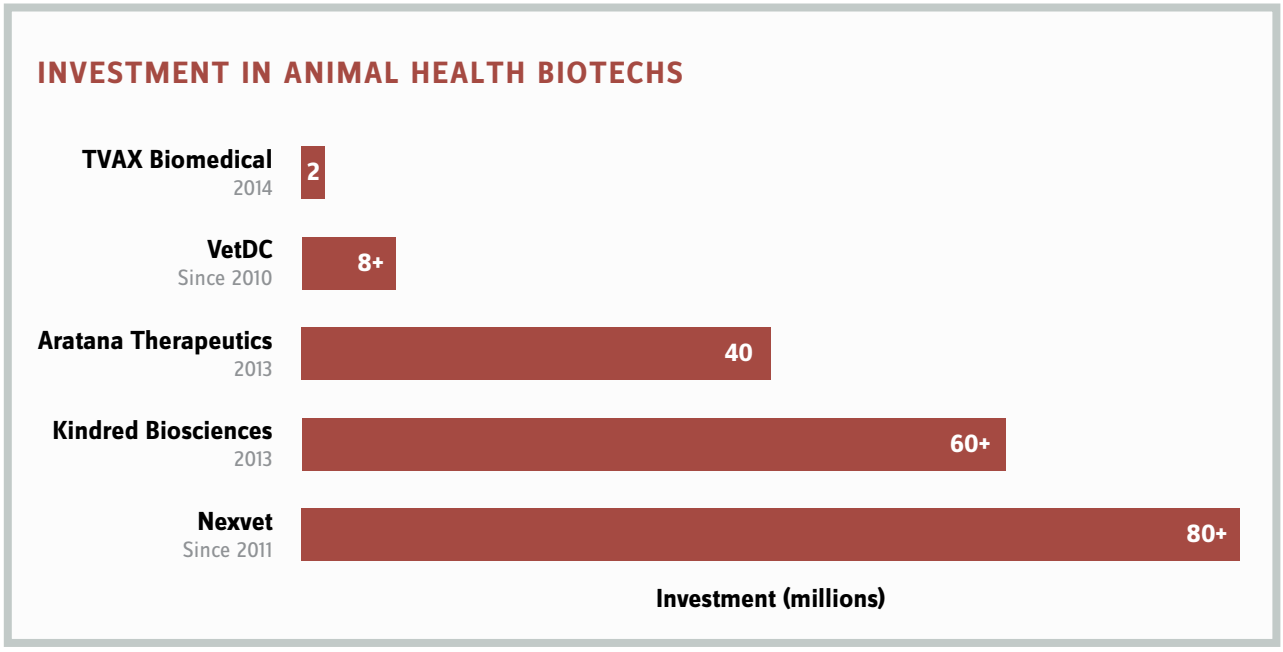
If the FDA authorizes VetDC's Tanovea, now under review, it will be the first approved canine drug for lymphoma, one of the most common cancers in dogs. VetDC licensed Tanovea from California-based Gilead Sciences, which evaluated the compound in preclinical studies with dogs with lymphoma at CSU. "Tanovea was highly efficacious and generally well-tolerated in dogs," says Roy. "However, Gilead decided not to advance Tanovea after early clinical studies in human patients revealed unanticipated side effects." When a CSU veterinary oncologist told him that Tanovea was a very promising new drug for canine lymphoma, Roy and his CSU colleagues leveraged their Gilead connections to license the compound for use as a pet therapeutic.

Tanovea fit VetDC's criteria because Gilead's preclinical studies had generated an abundance of data, providing the basis for the company's safety and efficacy submission to the FDA. "By focusing on shelved human assets, VetDC avoids pricing challenges often seen between pet and human medicines in order to introduce affordable drugs for pet owners," says Roy.

PET CANCER: A PRIORITY TARGET

In addition to conducting safety studies of Tanovea

> *"We can move from drug lead identification to safety testing and preliminary efficacy studies in about 18 months."*
>
> **MARK HEFFERNAN, PH.D.**
> CEO, Nexvet



in cats with lymphoma, VetDC is currently developing a second cancer compound, VDC-597, acquired from Pathway Therapeutics in 2013 before it closed its doors. As the leading cause of death in dogs and cats, cancer is a priority target of most pet biotech companies. Elias Animal Health has clinical trials underway to evaluate its autologous cell therapy, Elias Cancer Immunotherapy (ECITM), in dogs with osteosarcoma and B-cell lymphoma. "With continued positive outcomes from our trials, we anticipate significant interest in ECITM because of the limited treatment options for osteosarcoma and other forms of cancer that are available in veterinary markets," says Wahaus.

ECITM was designed by Elias' parent company TVAX Biomedical, which plans to initiate its Phase 2b clinical trial of the compound in human patients with glioblastoma in 2017. "In addition to bringing a much needed cancer therapeutic to the veterinary market, Elias' efforts will advance the proof of concept that TVAX's unique approach to immunotherapy could be effective in multiple cancers in humans," Wahaus says. "Many types of naturally occurring cancer in dogs are similar to the same cancers in humans. So it was logical for us to take a comparative oncology approach to accelerate the development of drugs in our TVAX pipeline." *(See sidebar on One Health.)*

Aratana's clinical trial of a therapeutic cancer vaccine in dogs with osteosarcoma has helped advance the clinical development of a similar therapy in children with newly diagnosed, nonmetastatic, surgically resectable osteosarcoma. The Aratana cancer vaccine, AT-014, is now under review at the USDA. AT-014 is based on a drug that Aratana licensed from New Jersey-based Advaxis. In 2016, the FDA granted fast-track designation for the Advaxis immunotherapy.

Aratana also has two canine-specific mAb cancer therapies, Blontress for B-cell lymphoma and Tactress for T-cell lymphoma. Because post-approval studies indicated that neither drug was likely to be as effective in combination with multi-agent chemotherapy as previous research had suggested, Aratana announced in September 2015 that sales of Blontress and Tactress would be modest. In the wake of that announcement, Aratana's shares fell nearly 39 percent. But, by September 2016, with its three FDA approvals and deal with Eli Lilly, Aratana's share price had recovered to well above its IPO price.

In human patients with several types of cancer, programmed cell death protein 1 (PD-1) inhibitors such as Keytruda and Opdivo have proven both safe and effective. Thus, Nexvet jumped at the opportunity to work with Zenoaq on "PETizing" the Japanese animal health company's PD-1 inhibitor, a rodent mAbs, to be native to dogs. Nexvet recently initiated safety, pharmacokinetic, and immunogenicity studies of the canine PD-1 inhibitor, which the company hopes will receive a conditional license from the USDA in three years.

In early 2016, Aratana began building a commercial infrastructure in anticipation of regulatory approval of its three pipeline drugs. VetDC, Elias, and Nexvet are in the early stages of planning the marketing, sales, and distribution of their drugs. "The animal health market is large enough to accommodate multiple competing small biotech companies," concludes St. Peter.

How Boehringer Ingelheim Is **Redefining Its R&D Strategy**

ROB WRIGHT Chief Editor @RfwrightLSL

In November 2015, Boehringer Ingelheim (BI) announced its new five-year R&D strategy, which included a commitment to invest $11 billion. Clive Wood, Ph.D., SVP of discovery research at BI, sat down with Life Science Leader to explain how the company is redefining its R&D strategy in order to maximize internal potential and expand research "for and beyond therapeutic area borders."

WHY HAS BI DECIDED TO REDEFINE ITS DISCOVERY RESEARCH STRATEGY?

We've had a number of strategic initiatives (e.g., Disease Map 2025 looks at aligning diseases, unmet medical need, and scientific opportunities), but I think we've gotten to a point where the next step needed to be transformative. In the past, we had a very function-based organization. And while this was very successful, our goal now is to evolve into an organization that is more customer-centric, which requires being flexible and agile and based around innovation units as well as therapeutic areas. In addition, we realize that many innovations come from the outside world. So in our redefined model, we wanted to communicate better across internal therapeutic areas and have more significant engagement externally.

DESCRIBE THE NEW DISCOVERY RESEARCH STRATEGY.

It is collaborative and involves three guiding principles:

- Building on our strengths
- Creating synergies
- Capturing emerging science

To build on our strength, we are focusing on four key therapeutic areas:

- Cardio-metabolic diseases
- CNS diseases
- Immunology and respiratory diseases
- Oncology

Despite identifying these four key therapeutic areas within BI, our goal is to build synergies in and across these different areas where diseases have common mechanisms, which I'll elaborate on more a bit later. One of the first things we did was to create one global cardio-metabolic disease research function (located in Biberach, Germany, and Ridgefield, CT) by merging two units that previously operated somewhat independently (i.e., cardiovascular and metabolic diseases). The idea behind this is that better metabolic disease outcomes require being cognizant of the role played by cardiovascular complications. We are exploring things such as nonalcoholic steatohepatitis (NASH) and obesity, just to name a couple. To broaden our presence here, we have embarked on a series of new partnerships (i.e., Circuit Therapeutics, Hydra Biosciences, University of Michigan and ETH Zurich, and the NIH), as well as asset acquisitions (e.g., Pharmaxis' PXS4728A for NASH).

We also combined the respiratory and immunology/inflammation departments into one new global therapeutic research area called immunology and respiratory diseases. The core of our research is focused on four key themes:

- Immune checkpoint modulation
- Dysfunctional innate immune effector function
- Aberrant tissue remodeling
- Mucosal barrier injury and repair

Some of the key collaborations in this therapeutic area include partnerships with the Icahn School of Medicine at Mt. Sinai, Mass General, Scripps Research Institute, and Weill Cornell School of Medicine.

With CNS diseases, we are focusing on key symptom domains, such as cognitive impairment and impulsivity, and are using tools like electrophysiological imaging and optogenetic methodologies to link symptoms and behaviors. Some of the companies helping us with our CNS research initiatives include Circuit Therapeutics and Arena Pharmaceuticals.

Finally, BI's oncology research therapeutic area has two primary fields of focus:

- Immune cell-directed therapies (e.g., tumor-specific T cells, cancer vaccines)
- Cancer cell-directed therapies (e.g., growth signaling, epigenetic regulation)

Some of the key oncology collaborations include the University of Texas MD Anderson Cancer Center, Vanderbilt University, Eureka Therapeutics, CureVac, and ViraTherapeutics.

While our discovery research department's geographical footprint did not necessarily change, our philosophy of how we work did. And while I would say we have many leaders actively involved in the planning of these strategic initiatives, it wasn't the approach of developing something "on high" and then trickling it down, but more of an inclusive approach involving all levels.

"One of the first things we did was to create one global cardio-metabolic disease research function."

CLIVE WOOD, PH.D.
SVP Discovery Research,
Boehringer Ingelheim

HOW DID YOU START THE PROCESS OF REDEFINING THIS STRATEGY?

When we first began, I had only been on board for about six months, and the first thing we did was to assess the landscape. As previously mentioned, we started by developing a set of guiding principles (i.e., building on our strengths, creating synergies, and capturing emerging science). We focused on the science, not technologies. For example, I feel very passionately about immunology and mechanisms of inflammation, as these are central to a wide range of therapeutic areas. This is why we opted to build an internal platform that facilitated this. So while we have biologists focused on therapeutic area research within specific disciplines, at the same time we have a group that works across the therapeutic areas to focus expertise and resources.

While the platforms create synergies internally, our new Research Beyond Borders (RBB) widens our view to target external science and technology. This group is charged with working globally across all research sites and therapeutic areas. We are locating "scouts" in strategic innovative hot spots around the world (e.g., Boston) and anticipate adding others as well. The RBB team aims to create new capabilities for BI's drug discovery and development in areas such as the (gut) microbiome, hearing disorders, regenerative medicine, and gene therapy. The RBB team already has established a multi-institute collaborative research model that brings together leading microbiome experts to study intestinal barrier disruption and enhanced permeability through an iterative process of bacterial stimuli, activation of host immunity, and exacerbation of chronic tissue damage. In Japan and China, RBB launched projects with experts in regenerative medicine from Kyoto and China Southeast University to explore hearing loss, the most common form of sensory impairment.

BEYOND RBB, WHAT ELSE IS BI DOING TO REDEFINE RESEARCH DISCOVERY?

There has been an increase in precompetitive public-private partnerships (PPP). BI is working with several PPPs in defined areas with a goal of sharing the results. Believe it or not, we have been active in 27 different projects. For example, we have contributed in excess of $33 million to the EU's Innovative Medicines Initiative (IMI) to discover new biomarkers, improve drug safety, and better engage with patients. BI is also an active member of the Structural Genomics Institute (SGC) which facilitates open-access research. Other PPPs critical to our research discovery efforts include the Division of Signal Transduction Therapy (DSTT) and the GPCR Consortium, which is coordinating studies of medically important proteins known as G-protein coupled receptors, while making the data available publicly.

We also have pursued several crowdsourcing projects (e.g., studying new translation models of psychiatric diseases, novel hypotheses on the contribution of epigenetics to respiratory diseases) and are working closely with brokers and incubators to discover novel therapeutic concepts. L

Cell Therapy Regulations Approach Their Inflection Point

GAIL DUTTON contributing writer @GailDutton

The need for discussions regarding guidelines for the development of therapeutics made from human cells, tissues, and cell- and tissue-based products has been building for a long time.

That need was evidenced by introduction of the REGROW Act (S. 2689/HR 4762) in Congress last spring, which tries to streamline commercialization of cell therapeutics, and by two days of public FDA hearings this past fall to clarify guidelines for cell-based therapeutics. "There's a huge wave of interest from patients, patient advocates, and the drug development industry," says Karine Kleinhaus, M.D., divisional VP for North America at Pluristem Therapeutics.

Opinion is divided between those who see expedited approval as a way to access potentially life-saving medications earlier and those who warn of the consequences of allowing safe, but possibly ineffective, therapeutics on the market.

"The current paradigm for cell therapy products was put in place nearly 20 years ago," notes Jay Siegel, M.D., chief biotech officer and head of scientific strategy and policy at J&J. "It's a fundamentally sound structure that tries to anticipate, classify, and regulate products for today and for the future."

But just as the science and the business of cell therapy have evolved, so have the questions. "The diversity of cell therapy products today is enormous, ranging from classic tissue banking and reproductive medicine to genetic modification and stem cells development," says Siegel. Regulatory nuances affect each of these therapies differently and have led to a complex, sometimes arbitrary, regulatory process.

THE FDA NEEDS GREATER CLARITY

"Companies need a clear, defined pathway to approval," Kleinhaus stresses. "Regenerative medicine developers currently lack regulatory clarity and the confidence that the development path they embark on will be deemed correct by regulators at the end of a program."

The Alliance for Regenerative Medicine (ARM) is among industry leaders calling on the FDA to list more examples of the extent to which a tissue's structure must be preserved to qualify as "minimally manipulated." It also recommends specifically listing centrifugation as a minimal manipulation technique except when it changes the character of the cells.

The term "homologous use" also lacks clarity. ARM suggests additional language distinguishing between structural and nonstructural cells, standardizing the meaning of "same basic function" within the guidance, and defining how the homologous-use provision should be applied to wound healing.

Each of those changes is intended to decrease confusion and enhance predictability. "Ensuring regulatory predictability is the most important aspect for updated guidelines," Siegel says. At the FDA hearings, J&J advocated for companies to receive a product designation from the FDA's Tissue Reference Group without disclosing confidential information on a public website. "We want the process more interactive so nuances can be discussed between agency and sponsor," he explains. Additional points include making more of the information public so companies with similar products can see a decision, know why it was made, and apply that information to their own regulatory submissions. Ultimately, such information could be formalized and incorporated into an FDA guidance.

JAPANESE LAW LAUNCHED DISCUSSIONS

Japan's Regenerative Medicine Law, passed in 2014, often is used as a model for expedited commercialization in this debate. That law triggered the development of the REGROW Act, which in turn helped catalyze the FDA hearings on cell therapy guidances.

After the REGROW Act was introduced, FDA hearings were scheduled, but public interest was so great that the time allotted for the hearing was doubled and

the date rescheduled months later. More than 90 individuals presented statements at the hearing. That overwhelming response provides regulators a broad look at the real-world issues complicating the development of cellular therapies today.

Japan's Regenerative Medicine Law was aimed to bring regenerative therapies to patients quickly. "It's inappropriate to characterize Japan's law as a shortcut, though," says Gil Van Bokkelen, Ph.D., chairman and CEO of Athersys. "I have first-hand experience with the Japanese Regenerative Medicine Law, and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) has very high standards and rigorous requirements."

Recalling meetings with the PMDA, Van Bokkelen says they discussed every ingredient used in the studies and later in manufacturing, trial designs, endpoints, and what evidence means in terms of product characterization, safety, and efficacy. "That meticulousness and the ability to incorporate data from international studies enables Phase 1, 2, and 3 trials to be compressed," he explains.

> *"A patient's own tissue, used to promote healing, should not be regulated as a drug."*
>
> **KRISTIN COMELLA**
> CSO, U.S. Stem Cell

REGROW COMES UP SHORT

The REGROW Act does not mimic Japan's Regenerative Medicine Law, and industry leaders have been outspoken. "Its intentions are good, but the details are lacking," notes Miguel Forte, chief commercialization officer for the International Society for Cellular Therapy (ISCT). He explains the REGROW Act contradicts existing FDA guidelines, ignores some of the more advanced forms of cellular therapy, and generally is less focused than agency guidances. "It creates confusion."

"The REGROW Act suggests that FDA review and approval processes need a complete overhaul, and that special pathways need to be created for cellular therapies," says Michael Werner, executive director of ARM. "We disagree." Instead, he advises evaluating the existing approval pathways to make them more effective by considering the needs and issues of each type of cell therapy. "There's no need to start over."

The most damning charge, however, is that the REGROW Act unintentionally creates a pathway for conditional approval without providing an efficacy standard. "There's a real concern from the cell therapy industry, investors, and academics that bad outcomes caused by underregulation will undermine the development of effective therapies and erode public confidence in regenerative medicine," Siegel says.

The REGROW Act almost certainly will die in committee, but it may be a stepping-stone to more informed regulations. As Siegel says, "Several changes have been discussed [but not formalized] that soften its rough edges by excluding gene therapy or nonhomologous uses, but it remains objectionable to many parties."

EXPEDITED COMMERCIALIZATION BENEFITS SOME

Some organizations do favor an expedited commercialization process. For example, because U.S. Stem Cell, Inc. develops a culture-expanded product rather than a minimally manipulated one, "the REGROW Act would be beneficial for us, allowing faster commercialization," says Kristin Comella, CSO for U.S. Stem Cell. "A patient's own tissue, used to promote healing, should not be regulated as a drug," she continues. Doing so would place unrealistic burdens on physicians. For instance, the double-blind placebo trials common in drug development would be cost-prohibitive and virtually impossible for physicians pursuing autologous cell therapies. Even most biotech companies wouldn't have the funding for such trials.

Without a product to justify the expense, there's little incentive for any organization, except perhaps the NIH, to conduct the research. Instead, autologous therapies evolve similar to other medical procedures, with details being disseminated through medical journals and with pioneering physicians gradually adopting them. Eventually, those therapies may become sufficiently mainstream to be reimbursed by third-party payers. Given that, Comella says, "Medical boards should provide oversight for autologous cell therapies like they do for skin grafts and other procedures. An attempt by the FDA to regulate the use of autologous tissue may be overreaching."

WHAT'S NEXT?

Final guidances for therapies made from human cells, tissues, and cell- and tissue-based products may not be issued until late 2017. Werner predicts these discussions will also feature in the 2017 Prescription Drug User Fee Act (PDUFA) hearings.

Although there is an overwhelming call for greater clarity, other details involving the regulation of cell therapy products remain to be resolved. Even the need for a new, expedited approval pathway via the REGROW Act is questioned. Instead, the prevailing sentiment within the industry is that the FDA already has the tools to facilitate expedited development of appropriate therapies. The next step is for the FDA to incorporate the key points from the hearings into guidelines that reflect the current knowledge and technology, so they remain relevant for at least a few years. The issues under discussion are complex, and changes in FDA guidelines, therefore, will likley not be swift.

Orphan Drug Incentives & Innovations On The Rise

ANGI ROBINSON

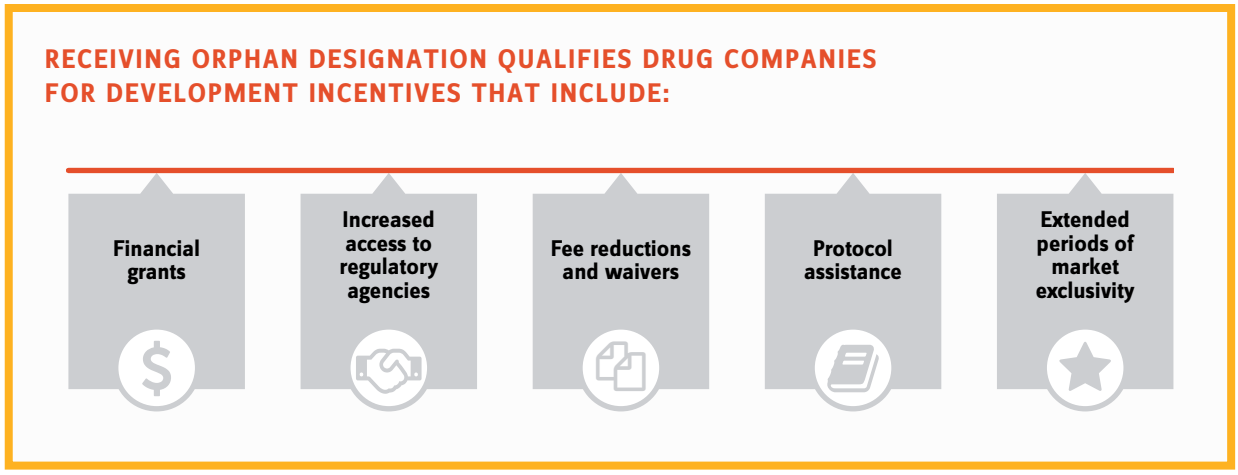
The year 2015 was a productive one for introduction of drugs that target rare diseases. U.S. regulators approved 21 new orphan drugs, a 40 percent increase from the previous year. European regulators approved a record 18 orphan compounds, a small increase over 2014.

Any progress is a good thing, but these advances pale when weighed against the enormous unmet need for rare-disease treatments. Worldwide, an estimated 350 million people suffer from rare disease, a list of afflictions that numbers more than 7,000 and grows year by year. Rare disease advocacy group Global Genes says about 30 million Americans — nearly one in 10 — live with a rare condition. In Europe, the percentage is about the same. Rare disease, thus, is largely a misnomer: While no single condition affects a lot of people, the sheer number of diseases makes for significant medical and societal impact.

And as troubling as these figures are, more sobering still is the fact that half of these diseases affect children. Yet for all the need, there are only about 400 approved orphan therapies. That means 95 percent of rare diseases go untreated, a fact that reflects the time and expense involved in developing these drugs and proving their efficacy.

Since passage of the U.S. Orphan Drug Act in 1983, regulators have provided extensive guidance and resources to support rare disease research. Receiving orphan designation qualifies drug companies for development incentives that include:

- Financial grants
- Increased access to regulatory agencies for scientific support and interaction
- Fee reductions and waivers
- Protocol assistance
- Extended periods of market exclusivity



Streamlining trials for a rare disease product takes a specialty logistics partner with worldwide infrastructure and local expertise. Additionally, an effective market access strategy, combined with a high-touch approach to reimbursement and clinical support creates the treatment lifeline. Designing a commercialization strategy, including distribution and third party logistics services, with the patient's comprehensive experience in mind takes a partner who understands that every patient matters. It takes AmerisourceBergen.

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The FDA and EMA (European Medicines Agency) are giving unprecedented support to addressing this vast unmet need, aiming these efforts largely at the biotech and specialty pharma companies that are at the forefront of orphan drug development. Many of these companies are very small, their fortunes in some cases tied to a single compound. Thus, they lack the resources to research and make best use of what's available to them. The following are some of the provisions set up to further their efforts.

"U.S. and European leaders clearly recognize the urgency in promoting development of orphan drugs and are committed to making the subject a continued high priority."

DEVELOPMENT GRANTS

Last fall, the FDA awarded 18 research grants, averaging just over $1 million each, for rare disease product development. They include:

- A $1.1 million grant funding continued development of a drug that makes tumor cells in HPV (human papillomavirus) patients more susceptible to immunologic attack
- $1.6 million in FDA funding that supports development of a vascular-targeted prodrug to treat recurrent glioblastoma
- FDA initiatives such as the Orphan Products Natural History Grants Program, which in fiscal 2017 will fund $2 million in rare disease-related natural history studies

The EMA, meanwhile, is two years into Horizon 2020, its largest-ever research and innovation program and one of the biggest such endeavors worldwide. Horizon 2020 has committed nearly 80 billion euros through 2020 to promote scientific excellence and strengthen industrial leadership.

EARLY ENGAGEMENT WITH REGULATORS

More than 90 percent of the drugs that reach clinical testing fail. With the deck so heavily stacked against them, drug developers have to seize every advantage available to them. Fortunately, U.S. and European regulators increasingly seek earlier involvement with sponsors, and most are embracing the opportunity.

At a recent industry conference in Europe, an EMA representative exhorted sponsors to engage early to ensure efficient and scientifically rigorous processes. One avenue for early involvement is EMA's Innovation Task Force, an information platform for early dialogue on scientific, technical, and regulatory issues. The FDA is always willing to talk with sponsors prior to study startup. Sponsors can request formal Type B (pre-IND, end of Phase 2a) meetings or Type C (general guidance) meetings throughout product development.

PRECOMPETITIVE COLLABORATION

Sponsors increasingly employ a process called *precompetitive collaboration*, working with government organizations, academic research centers, and even competitors. Rare drug researchers take on extremely complex challenges with very limited data, a mixture that makes their pursuits time-consuming and expensive — and inevitably yields a poor success rate. Precompetitive collaboration played a major role in HIV/AIDS research as competing pharma and biotech companies joined with academic researchers and government research institutes to answer a challenge that demanded the best of their collective ingenuity.

The importance of precompetitive discourse prompted the 2014 launch of the Accelerating Medicines Partnership. AMP, a public-private partnership among the NIH, FDA, 10 biopharmaceutical companies, and several nonprofit organizations, seeks to transform the current model for developing new diagnostics and treatments by identifying and validating promising biological targets for therapeutics.

U.S. and EU regulators are collaborating to an unprecedented degree. The FDA and EMA have greatly increased their level of cooperation and information-sharing in recent years, have regular interactions, and maintain structured scientific and regulatory working groups, or "clusters." A patient engagement cluster created in 2015 shares experience and best practices around patient involvement in drug development, evaluation, and postauthorization activities.

IMPROVED ACCESS TO GOVERNMENT DATA

Hundreds of data-sharing repositories house the results of scientific research funded by U.S. government agencies. Those agencies are making this wealth of information much more available to researchers. The U.S. Department of Health and Human Services in 2015 issued a public access policy covering its largest operating divisions: the FDA, the NIH, the Centers for Disease Control and Prevention, and the Agency for Healthcare Quality and Research.

The agency has two goals: to make publications

RARE DISEASE ADVOCACY GROUP GLOBAL GENES SAYS ABOUT 30 MILLION AMERICANS - NEARLY 1 IN 10 - LIVE WITH A RARE CONDITION

resulting from the research it funds freely available to the public and to make the information available in digital formats. (The digital infrastructure is still in its infancy.) HHS Secretary Sylvia Burwell declared this an inflection point in history in describing plans to give the public maximum access to, and value from, federally funded health research data.

TARGETING AN ULTRARARE METABOLIC DISEASE

Some of these efforts recently came together to advance treatment of hypophosphatasia, or HPP, a progressive, ultrarare metabolic disease for which only supportive medication previously was available. The disorder is characterized by abnormal development of bones and teeth, the result of defective mineralization — the process by which bones and teeth take up minerals such as calcium and phosphorus. Patients have bones that are soft and prone to fracture and deformity, and defective mineralization of teeth can lead to premature tooth loss.

A U.S. pharmaceutical company sought to treat the condition with asfotase alfa, an innovative enzyme replacement drug. The FDA granted the compound Breakthrough Therapy designation and issued the developer a Rare Pediatric Disease Priority Review Voucher, which confers priority review to a subsequent drug application that would not otherwise qualify for priority status. The voucher program encourages development of new drugs and biologics to prevent or treat rare pediatric diseases.

Meanwhile, the EMA conferred orphan status and provided scientific advice through its Committee for Medicinal Protocols for Human Use.

The expedited development and subsequent approval of the drug — now approved in the U.S., European Union, Japan, and Canada — reflects the growing promise in the battle against rare diseases. The concerted efforts of governments, regulators, and industry provide the best hope for encouraging development of new therapies, opening doors, and giving hope to the hundreds of millions who suffer from these conditions.

OTHER GOVERNMENT ACTIONS

Legislators are joining the regulatory community in taking up the cause. The 21st Century Cures Act, introduced in May 2015, seeks to accelerate the pace at which the FDA approves new medicines for conditions currently lacking cures — along with a lengthy list of other proposals. The act passed the House of Representatives with overwhelming support but remains stalled in the Senate, which has introduced a number of separate companion bills.

Another prominent government initiative arrived in early 2016 as the Cancer MoonShot 2020, a coalition that is pursuing vaccine-based immunotherapies to fight cancer. Combining the resources of pharmaceutical and biotech companies, academic centers, and oncologists, it promotes access to more than 60 novel and approved agents now under exploration.

Government action can prompt regulatory change, but doesn't necessarily need to precede it. U.S. and European leaders clearly recognize the urgency in promoting development of orphan drugs and are committed to making the subject a continued high priority.

ANGI ROBINSON is executive director, pediatrics and rare diseases at Premier Research. She has worked in clinical research for over 15 years providing executive oversight and full management support for global clinical trials with a focus in pediatrics and rare diseases.

Biotech Bounces Back: A Tale Of Two Companies

GAIL DUTTON Contributing Writer @GailDutton

Double down, forge a new direction, or throw in the towel for your current project. Those are the options for surviving setbacks. Which approach you take may not matter without a clear and unemotional understanding of your company and its science.

Here's a look at how two biotech companies faced their challenges and are bouncing back.

18 YEARS OF BOUNCING BACK

Oncolytics Biotech has been developing Reolysin as a cancer therapy for 18 years, based on the oncolytic properties of the reovirus. When this single-product company faced delays, it doubled down, going deeper into the science to learn more about its lead compound's mechanism of action.

As Brad Thompson, Ph.D., CEO of Oncolytics, points out, (editor's note: Dr. Thompson stepped down while this article was in production. Dr. Matt Coffey has been appointed interim president and CEO while the company conducts a search for Dr. Thompson's replacement.) developing first-in-class therapies takes longer than more established approaches because of the combination of unknown or lesser-known mechanisms of action and new manufacturing methods. "The industry's first cancer antibody took about 20 years to be commercialized," he points out. By that timeline, Oncolytics is right on schedule.

Phase 2 trials began for Reolysin in 2001 in Canada and the following year in the United States. "If we had pushed ahead into Phase 3 trials immediately after completing Phase 2, the trials would have failed because we didn't understand the mechanism of action then," Thompson says. Delaying Phase 3 trials gave his team time to learn that this oncolytic virus has a dual mode of action, working as a cytotoxic agent to reduce the tumor burden while also stimulating the immune system.

Researchers also learned that the therapy has a significant gender bias, tripling therapeutic improvements in women with colorectal cancer. It also appears effective in treating metastatic disease. "Most studies don't consider those areas," Thompson says. Focusing on the underlying biologics allowed genomics to mature, so researchers may predict clinical responses for specific patients.

In its early days, Reolysin was directly injected into prostate tumors during Phase 2 trials. "The study results looked great, but none of the patients were willing to return for a second treatment," Thompson recalls. Therefore, intravenous delivery was considered. "The FDA said 'no way,' so we went to the U.K. to conduct trials to define dosage and learn where the drug actually went in the body." (It clears preferentially in the liver and crosses the blood-brain barrier.) With that knowledge, "we can conduct trials for pediatric brain cancers in the U.S." Reaching that point took about seven years.

Trial design also affected outcome. "In a double-blind study in the U.S., we found patients dropped off the test arm because of low-grade fevers, which prevented the study from progressing," Thompson recalls. Patient dropout wasn't an issue, however, for the 13 open-label studies of head and neck cancers conducted in 13 other countries.

Additional delays were caused by the desire to learn which drugs, administered with Reolysin, sup-

"We were almost out of business at one point. Investors get weary."

BRAD THOMPSON, PH.D.
Former CEO of Oncolytics

ported viral replication and which prevented replication. Without viral replication, the therapy couldn't work. Testing every known chemotherapeutic agent — including checkpoint inhibitors and other emerging therapies — cost $100,000 per patient and involved 500 patients. "Completing those investigations took about seven years," he says.

Afterward, Reolysin was granted orphan drug status in the U.S. in 2015 for pancreatic, gastric, ovarian, primary, peritoneal, and fallopian tube cancer, and malignant gliomas. It has orphan drug status in Europe for ovarian and pancreatic cancer. Phase 3 trials are expected to launch in the U.S. in 2017 for nonsmall cell lung cancer (NSCLC) and metastatic colon cancer.

WHY DOUBLE DOWN?

"We stayed with this drug because it worked," Thompson emphasizes. "Our first radiation therapy had a 100 percent response rate in tumors. Patient 2 of 1,100 still visits me." Without this treatment, that patient was expected to die 15 years ago. "That's why you stick with a product. Patients are alive because of our clinical studies."

Belief in a product or an approach is a powerful thing. "As CEOs, we convince investors to provide millions of dollars based on a concept. People invest in your company because you believe your approach will work. Over time, that conviction is converted into a belief based on data."

INVESTORS NEED AN ENDPOINT

Nonetheless, investors expect an endpoint. Stock prices for Oncolytics have fluctuated from a high of $20 (October 2000) to 30 cents Canadian (October 2016) on the Toronto Stock Exchange. Still, Oncolytics raised $19 million Canadian in 2015 and ended the year with $26.1 million in cash and cash equivalents — enough to support upcoming studies.

"We were almost out of business at one point," Thompson admits. "Investors get weary. That's an important factor to consider in conducting added research. Nobody believed it would take us this long, but they don't fault us for answering the questions we answered."

He says many biotechs have survived similar situations and cites Amgen as one example. "Amgen's management believed in what the company was doing. They plugged away, and one morning it had become one of the largest, most successful biotech companies in the world."

For Oncolytics, once Phase 3 studies begin, an endpoint will be within sight. Assuming the multiple myeloma study is a success, the company could file for marketing approval in about two years.

The decision to remain a single-product company had no effect on fundraising, Thompson says. "Half the fund managers are obsessive about sticking to what you know. They mitigate risk by buying multiple companies, so those companies needn't diversify. Once you have an approved product, that's the time to build a pipeline." The other half of investors prefer platform companies. In that scenario, "If a lead fails and the company trades low, the management team turns over, and a new company emerges with a new product."

WHEN EVERYTHING FAILS, REINVENT YOURSELF

That change that Oncolytics experienced is similar to the systematic reinvention that ultimately created Akari Therapeutics.

Akari's story begins with Morria Biopharmaceuticals. Gur Roshwalb, M.D., CEO, had worked as a physician, as a healthcare research analyst for a leading investment bank, and as an investor at a venture firm. To gain operational experience, he joined Morria as CEO when it was near bankruptcy. "I renamed it Celsus Therapeutics, raised $21.7 million and got the company listed on NASDAQ," he says.

Celsus Therapeutics' lead candidate, a topical anti-inflammatory drug for eczema dubbed MRX-6, failed to meet its endpoint in a Phase 2, showing no difference from placebo. "Even though we hadn't pursued the technology we had, the company still had value," Roshwalb says.

At that point, Celsus was a NASDAQ shell with $3 million in unencumbered cash. Its most obvious option was a reverse merger. A merchant banker introduced Roshwalb to Volution Immuno Pharmaceuticals SA, a British firm that was interested in Celsus' NASDAQ listing and unencumbered cash. "Volution had promising Phase 1 data from Coversin, a small protein that inhibits the C5 complement, but it needed $45 million to advance to Phase 2 trials," Roshwalb explains. Volution's options were to pursue crossover financing or go through the lengthy IPO process. Merging

with Celsus provided a quicker path to the public market than an IPO. "We closed the reverse merger in September 2015, forming Akari Therapeutics PLC, and did a $75 million private investment in public equity (PIPE) at the same time, just before the IPO window slammed shut."

Roshwalb characterizes the deal as more of a marriage than a merger, albeit one that caused him to release most of Celsus' staff and divide his time between London headquarters and New York.

FOCUS ON KNOWN BIOLOGY

Akari abandoned Celsus' eczema product and instead is focused on a next-generation C5 inhibitor, developing a platform therapeutic for orphan autoimmune and inflammatory diseases. This drug, Coversin, could compete with Alexion's blockbuster drug Soliris in treating paroxysmal nocturnal hemoglobinuria (PNH). In September 2016, Coversin received orphan drug status from the FDA. If trials proceed as expected, Roshwalb predicts Coversin could be second to market, introducing an alternative with a similar mechanism of action for an underserved patient population.

The key difference between Akari and Celsus, Roshwalb says, is that Akari's drug has "a predicate biology that's well-understood." In contrast, the biology behind Celsus's MRX-6 anti-inflammatory was still being discovered.

Companies fail, Roshwalb says, "by throwing good money after bad." Failing quickly so companies can use their resources discovering what works is a goal in the biotech industry, but failures aren't always easily recognizable. And, if a company has only one drug, abandoning it generally means abandoning the company. "Too often, people are unwilling to accept what the data tells them. We could have said there was an outside response to MRX-6 and continued our research. Instead, we realized the drug didn't work and returned it to the university from which we licensed it."

FAILURE CAN BE GOOD

For Celsus, failure triggered a change in direction. For Oncolytics, it resulted in laying a stronger scientific foundation. Both approaches have resulted in better molecules.

"Failures are critical to success," Thompson says. "If something works every time, you don't know its boundaries." In learning those limitations, Oncolytics mined its data, discovering successes in subpopulations that may not have been considered if the drug had succeeded broadly in its early development.

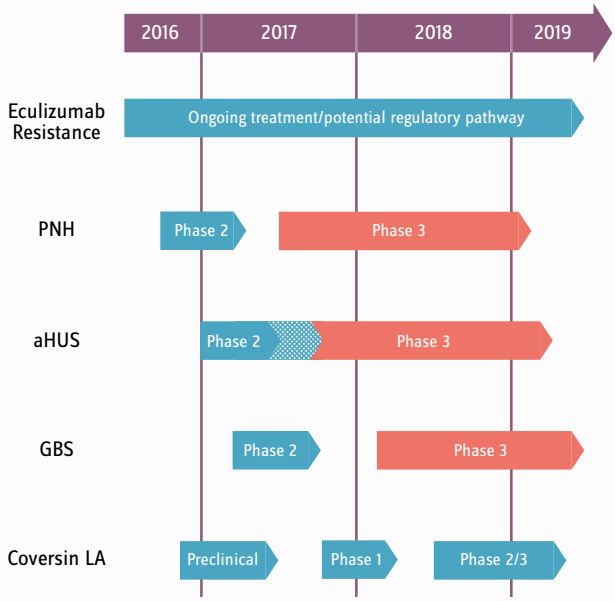
Oncolytics and Akari took dramatically different approaches to ensuring that, despite setbacks, their companies survived. With an industry failure rate of approximately 90 percent, their ability to advance candidates into late-stage clinical trials speaks to their abilities to view their prospects dispassionately and assess their options with clear heads. Whether Oncolytics and Akari successfully commercialize their lead candidates remains to be seen.

"Too often, people are unwilling to accept what the data tells them ... We realized the drug didn't work and returned it to the university from which we licensed it."

GUR ROSHWALB, M.D.
CEO of Akari Therapeutics

AKARI THERAPEUTICS PRODUCT PIPELINE

Current development stage for Coversin indications



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Janssen Uses Trial Simulations To Capture Patient Concerns

ED MISETA Chief Editor, Clinical Leader @EdClinical

Bert Hartog, Ph.D., innovation leader, in R&D Operations Innovation at Janssen Research & Development, has a plan in place to make trials more patient-friendly. Janssen's goal is to incorporate the patient voice into clinical research, make patients a partner in the research process, and ensure all future collaborations are a two-way street.

Today, it seems every sponsor wants to incorporate the patient voice into clinical research. But for most, the challenge is figuring out how to successfully capture that feedback. To ensure the Janssen effort was successful, Hartog knew the company needed a method to generate those patient insights that helped better define and enhance studies.

The approach needed to involve two aspects: protocol design and study execution. "Both are equally important," says Hartog. "You can design the best protocol in the world, but if you don't know how to run it, then it's going to be a failure. And you can run a study brilliantly, but if the protocol is not workable for patients and sites, it will likewise be a failure."

The company tapped into disease-specific and general patient communities, hoping to apply market research methods to generate research insights. While helpful, these efforts still weren't what Hartog considered to be "real" interactions. The problem was that the responses provided by potential participants were still far removed from the actual clinical trial.

TRIAL SIMULATIONS: A POWERFUL WAY TO GAIN INSIGHTS

When pondering this problem, a Janssen research team had the idea of a clinical trial simulation that would be an active exercise, much like a workshop, to truly understand how a study or proposed study will be received by patients and investigators.

Hartog says, "For us, this was a very powerful way to improve the design of the study. We were able to look into specific needs that came up during the simulation, but also look at logistics and other factors such as doctor/patient interactions that we normally may not spend much time thinking about."

Hartog hopes simulations will become more common in clinical trials. The feedback and insights from patients and investigators will certainly help sponsors to better design and execute clinical trials. But more importantly, the simulations will give patients confidence that a study was properly evaluated, tested, and refined before the recruitment process began.

AGE-RELATED MACULAR DEGENERATION: THE FIRST TEST

The first simulation performed by Janssen was done to prepare for a Phase 2 study and involved a group of patients who were new to the company. All of the patients were suffering from age-related macular degeneration, a disease that was also fairly new to the company.

Going in, the goal was simply to understand how the proposed clinical trial would be perceived by patients and investigators. Hartog hoped to get to know the patients better and understand the subtleties of the interactions taking place between clinical investigators and patients who were progressing to loss of vision.

"We got a lot of very useful feedback, but we also learned that the methods used to run a trial simulation are quite intricate," notes Hartog. "For example, we found you can't just go into a simulation and start observing the interactions between people. You need to

have a very thorough research plan in place. You need to spend time properly preparing the environment for the simulation. We also found you need to get the right individuals to participate, which includes patients, caregivers (dependent on the disease), investigators, and representatives from the sponsor company."

In terms of preparation, Hartog notes it was no different in a simulation than in a trial, especially when it came to compliance. Compliance is necessary to ensure the privacy of the individuals and to properly secure the data. Hartog recommends a company's internal compliance review team be involved from the very beginning.

"Getting compliance involved is something we do for every clinical trial," shares Hartog. "But for a new therapeutic area like age-related macular degeneration, coupled with a new feature like the simulation, it was still a different experience. We had people reviewing the compliance requirements who did not have prior experience to lean on to judge the merits of the approach. This is one area where the innovation team was able to help them understand what the simulation was about, what we were trying to accomplish, and how it would be different from an actual trial."

MORE SIMULATIONS PROVIDE ADDITIONAL INSIGHTS

The first age-related macular degeneration simulation helped Janssen better understand the trial and patient/investigator concerns. The company then set up two new simulations. One was to understand more about the protocol design for an upcoming trial and took a closer look at the burden placed on participating patients.

This second trial featured a protocol with a long list of skills assessments and questionnaires. There were also questions about the interactions between participants and investigators. Hartog knew that many patients find these questionnaires to be tiresome. "Completing the surveys and questionnaires can take three or four hours," he says. "We felt a second simulation would be an ideal opportunity to see when participants get tired or needed a break so that we could determine when best to stop the assessment or even schedule a follow-up visit."

While that may not seem like a major concern, Hartog notes that discovering this type of information during the trial could result in damage to the integrity of the data or force a company to halt the trial and redesign it. By determining a patient's fatigue level during the simulation, the trial can be designed with those insights in mind.

These first two simulations were organized in a market research center with see-through mirrors where researchers can observe participants without interfering in the workshop. The rooms were designed and equipped for that specific purpose and resembled an actual physician's office. This helped patients and physicians feel as natural as possible while still being in a market research facility.

The third simulation was for Alzheimer's patients. This simulation was conducted in a hospital, which Hartog believes was the first time a simulation was conducted in the same setting where the trial will take place.

The first two simulations mentioned also were conducted in just one country, one in the U.S. and one in the Netherlands. The Alzheimer's simulation was run in three countries: Spain, the Netherlands, and the U.S. This is because the Alzheimer's trial will be a multinational study.

"We felt doing the simulation in parallel in Europe and the U.S. would give us a good feel for potential differences in outcomes," says Hartog. "Based on the insights received, we could decide if we wanted to expand the study into South America and Asia or keep it confined to the U.S. and Europe."

Still, conducting the simulation in three different countries was a challenge. In fact, the complexity surprised Hartog. Clinical trials are generally conducted in a similar manner around the world. That is not the case with market research, which is done differently in various countries and regions. For Hartog, the challenge wasn't that it couldn't be done, but that it hadn't been done. Aligning the effort in Europe and the U.S. was a complexity he had to work through, to allow the same simulation to take place in different countries.

Additionally, two of the sites recruited patients from a 2a study to participate in a simulation with the 2b study. These individuals had experience participating in a trial and would be seen as experts in providing insights to the clinical trial process. Researchers were also able to determine if their insights were different from simulation participants who have never taken part in a study.

Hartog states simulations are best suited for Phase 2 and Phase 3 trials, noting Phase 1 trials are exploratory in nature, making the relevance of the simulation less impactful. Phase 2 and Phase 3 trials tend to be riskier, both in terms of potential failures and cost implications. They also involve substantially more patients.

"We felt doing the simulation in parallel in Europe and the U.S. would give us a good feel for potential differences in outcomes."

BERT HARTOG, PH.D.
Innovation Leader, R&D Operations Innovation
Janssen Research & Development

HELP FOR RECRUITMENT AND RETENTION

Recruitment and retention remain a challenge for pharmaceutical companies conducting trials. Any innovation that can make trials easier on patients will certainly help overcome this problem, and simulations are a step in the right direction.

Hartog believes future trials will show improved recruitment and retention based on the insights generated through simulations. In the age-related macular degeneration simulation, Janssen learned that patients appreciated the sharing of scientific information regarding their condition, along with models of the eye used with the explanations. This enabled them to not only listen, but to see the model, understand the problem, and know how the treatments would impact their condition.

Investigator engagement may also be improved by the simulations and could further impact patient recruitment. Hartog believes engagements with investigators will improve because of researchers observing their struggles and coming up with better solutions. For example, one issue for investigators is the informed consent process, and the learnings from the study can be used to better train investigators on how to approach informed consent conversations with patients.

Best of all, since the simulations are conducted by Janssen R&D Operations Innovation, the best practices learned will allow the company to build an internal knowledge base, or information repository. One study team might be running the simulation, but they are not the only ones who will benefit from it.

"This is not information that will be available for only one-off use," adds Hartog. "Since it relates to the interaction between patients and investigators, it will be valid regardless of the therapeutic area and whether a study is performed in-house or outsourced to a CRO." L

Beyond Oncology — Precision Medicine For Autoimmune Diseases

DR. GEORG LAUTSCHAM AND DR. STEFAN MÜLLNER

Precision medicine (also known as personalized medicine) offers a more efficient mode of drug development for the pharmaceutical industry, as well as promising more-effective therapeutic tools for physicians and better outcomes for patients.

While it has been reasonably well-applied in the field of oncology, the ongoing development of novel technologies and changes in the regulatory landscape are essential if the approach is to be effectively applied to other important therapeutic areas.

THE NEED FOR PRECISION MEDICINE

Drug development is a risky and expensive process; an analysis published in 2016 by the Tufts Center for the Study of Drug Development cited an estimated cost of $2.5 billion to take a drug to market. In addition, most of the drugs that do make it to market only work on a fraction of patients, which is causing regulators and payers to reconsider which drugs should be approved for clinical use and reimbursed by the healthcare system. For example, the 10 highest-grossing drugs prescribed today in the U.S. are effective on just 25% of recipients. This suggests that our ability to match the right patient with the right treatment is poor and that improvements need to be made.

One promising approach for overcoming this challenge is precision medicine. At its core, it uses specific molecular diagnostics and biomarkers to stratify patients into more discrete disease subsets. This knowledge can enable researchers to identify exclusive molecular drug targets likely to be important within a given disease subset, so that they can develop new compounds against them. The idea is that the more tailored the treatment is toward a certain subset of patients, the more effective it will be.

Molecular biomarker data also can support the development of new companion diagnostic (CDx) tools designed to profile patients based on the molecular characteristics of their specific disease subset. These can then be used to predict whether a patient will respond favorably to a treatment and anticipate any potential adverse reactions before it is administered.

A HISTORICAL FOCUS ON CANCER

To date, oncology has been the field to benefit most from precision medicine. The textbook example is Herceptin, which targets human epidermal growth factor 2 (HER2) receptors and is only administered to patients who overexpress the receptor. The drug's success came to embody the notion that better characterizing a particular disease phenotype at the molecular level, and subsequently developing therapies and diagnostic tools that exploit this knowledge, is an effective way of boosting treatment response rate. In fact, the overwhelming majority of cancer drug development programs today are based on patient stratification guided by biomarker analysis.

So why has most of the focus been on cancer? First, for many years, if not decades, cancer research has received significant financial investment compared to other diseases, both within academia and the pharmaceutical industry. This is mainly because a cancer diagnosis was formally considered a death sentence, and U.S. President John F. Kennedy initiated a research campaign to identify a cure for cancer. This initiative was the start of a global research effort, which has since increased our understanding of the genetic complexity underpinning the wide range of disease subsets we classify as cancer and opened our eyes to the true molecular diversity of the disease. In turn, research-

ers have been able to use information from genome sequencing and genomics technologies to better stratify patients into subgroups (as well as develop new drugs and diagnostic tools to treat them). Secondly, at a time when treatment responses for cancer therapies were very low (5 to 20 percent), regulatory bodies encouraged pharmaceutical companies to invest in biomarker-driven approaches to enhance patient stratification and improve patient outcomes.

While there has clearly been significant progress in applying precision medicine to cancer, other disease areas have lagged behind. For example, autoimmune diseases have significant economic and social impacts and represent the second-most important market for pharmaceutical companies, which is unsurprising when you consider that, while 1 in 33 Americans will suffer from cancer, 1 in 6 will suffer from an autoimmune disease, costing the U.S. over $100 billion a year. However, the uptake of precision medicine in this area has been slow at best, even though it can be extremely difficult to accurately diagnose and treat patients effectively using the tools that are currently available.

APPLYING PRECISION MEDICINE TO AUTOIMMUNE DISEASES

There are three main factors that can drive the widespread adoption of precision medicine for treating autoimmune diseases: increased research funding, greater regulatory pressure, and the development of new technologies to enable better patient stratification.

The first two mirror what has happened in oncology over the last few decades and will rely upon a shift in mindset among stakeholders such as policy makers, funding bodies, healthcare providers, and the pharmaceutical industry as a whole. Promisingly, the wheels may already be in motion, with the FDA having released a guidance paper in July 2016 recommending the codevelopment of novel therapies and corresponding CDx in all disease areas.

Autoimmune diseases also require different technology platforms for molecular characterization, as they are fundamentally dissimilar in nature to cancer. For example, many cancers can be attributed to specific changes in a patient's DNA that can be detected using techniques such as PCR (polymerase chain reaction) and DNA sequencing, which themselves have been the source of concerted research efforts to increase their sensitivity and specificity. These methods are now so sophisticated that they can be used to detect and analyze circulating tumor DNA molecules that have been shed into a patient's bloodstream, even when only a few copies of the mutant DNA are present. Furthermore, they are now considered relatively cheap, easy-to-perform, and highly reliable, making them a regular feature of cancer drug research and clinical trials.

Sadly, the pathology of autoimmune diseases is usually much more intricate, and the onset of these diseases is rarely triggered by a series of genetic mutations. Instead, the term encompasses a wide variety of related maladies, all characterized by a complex, maladaptive response of the immune system (which begins to target the body's own tissues and organs through the generation of autoantibodies). It is this underlying process that provides us with a window of opportunity; the autoantibodies produced can often provide insights into how the disease will manifest and progress, making them viable candidates as biomarkers for the differential diagnosis of patients. In many cases, these autoantibodies are intrinsic to the disease itself and are often highly detectable (even in the early stages), while their ongoing expression patterns can give a strong indication of disease stage and severity.

If autoantibodies are excellent candidates for biomarkers in patients with autoimmune diseases, how can we account for their lack of adoption within clinical research and diagnostic development? The answer to this question may revolve around the technologies currently available for the systematic identification of novel biomarkers, many of which cannot offer the necessary sensitivity and specificity. In addition to this, the detection of multiple autoantibodies (sometimes as many as 10 to 15 as part of a multiplex panel) is required for the proper stratification of patients into meaningful disease subgroups.

If the adoption of precision medicine is to truly gather pace among diseases outside of cancer, there are still a number of regulatory, technological, and funding-related hurdles to be overcome. Taking lessons learned from within the field of oncology and systematically applying them to areas such as autoimmune disease will enable the development of more effective drugs across a wider range of illnesses. Most importantly, this will lead to a better outcome for patients. L

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Meeting The Unknown Need
In Pharma Labs

ERIC ROMAN

The very nature of many scientific processes creates habitual behaviors. Often these habits are effectively passed from senior lab generations to younger ones. Old habits can be hard to break, especially in a time-pressured lab environment. People don't often want to take the time to learn a new way of working or break attachments to their favored equipment, especially when the "old methods are working just fine." However, as laboratory leaders, it is critical to make meaningful changes to daily routines and the equipment used. It is the role of the lab managers, as the drivers of growth, to be able to identify areas for improvement and help their teams see the real value in a new way forward. Communication needs to be part of the everyday functioning — at all levels — to anticipate hurdles and identify solutions. Collaborative identification of challenges and improvements helps to set the foundation for buy-in and successful change.

While constantly being called upon to improve process efficiencies and boost outputs, senior management faces a significant challenge: how can productivity issues be addressed when lab teams are not even aware of their existence? Management needs to remain vigilant of the actions that need to be taken in the best interest of the output of the lab — even when change might not be popular.

DRIVING INNOVATION

Often researchers will adapt to current protocols, with a tendency to find workarounds that may alleviate particularly unfavorable conditions. However, this can be at the detriment to laboratory efficiency and cost. One customary workaround used by cell culturists is to avoid the outer 36 wells of a 96-well plate, which reduces capacity by 37.5 percent and, therefore, decreases throughput. Since evaporation is such a common issue researchers have faced, this has been a traditional technique to avoid problems in outer wells during prolonged culturing. This conventional process negatively impacts laboratory productivity, as more plates and assays are needed to compensate, which drives up costs. As this practice is seen as "normal," it is not usually perceived as a problem in the laboratory. This example is representative of the lab leader's responsibility to share new methodologies that circumvent this phenomenon. Researchers and lab technicians should remain focused on their work; it is management's responsibility to drive a more efficient, economical, and safer way to work.

EFFICIENCY THROUGH SAFETY

The driving forces within a lab are efficiency and safety. Constant oversight is conducted to create an environment where both exist. For example, when working with a standard instrument such as a manual pipette, users can be put at risk of repetitive strain injury or carpal tunnel syndrome due to the motions and forces needed during tip attachment and ejection. To help prevent overuse and injury, laboratory leaders need to provide an expert voice in the selection process of the equipment used in the workflow to bring about the best decisions for efficiency and safety.

Collaborative decision making will help to identify best practices and overcome staff habits to ensure productivity and safety. Ongoing education for awareness of alternative technologies contributes to productive change. A proactive stance on issues of safety also helps to protect the lab from future liability issues.

Establishing ongoing ways to boost productivity can prove difficult, especially when identifying hurdles is a challenge in itself. Providing an environment where change and growth are cultural norms allows for an openness to experimentation for best practices. Lab leaders are expanding their collaborative partnerships both internally and externally to increase productivity, streamline processes, improve safety, and deliver ongoing lab success. We need to be visionaries and take a longer view of the horizon to anticipate the future and actively seek options that stand to benefit the lab team and, by extension, the quality and timeliness of a laboratory's data output. L

ERIC ROMAN is president, laboratory consumables, at Thermo Fisher Scientific.

How To Increase Productivity Via Unconventional Hiring

HARVEY YAU

One of the most vexing and common problems HR professionals face is acquiring and training talent for specific skilled positions, only to see that talent, and the time and money invested in them, walk out the door too soon.

Scenarios like this have often impacted the global life sciences industry negatively. Let's examine the issue and explore a solution — one that has the potential to increase productivity and employee retention.

Research at www.biospace.com indicates life sciences companies are expected to hire 5.2 percent more new graduates from the Class of 2016 than they hired from the Class of 2015. Generally, nearly 25 percent of all posted job listings are at entry level, requiring zero to two years of experience. Bachelor's degree-level recent graduates will fill many of these jobs.

These graduates often find themselves assigned to repetitive tasks like quality control, bioprocessing, and manufacturing. Coming in, they may not have the up-to-date GMP training and requirements to be productive immediately. The problem is, close to 70 percent of these workers will leave before the eight-month mark. There are a lot of reasons why, but often it is that these well-educated workers have grown bored, they want a new challenge or a new title, or they feel they aren't advancing fast enough. Their leaving undoubtedly creates an investment deficit that adversely affects both profits and productivity.

MATCHING TALENT WITH TASKS IS THE ANSWER

So there's the crisis. Where's the opportunity? The key is to hire and utilize your workforce more intelligently — finding motivated talent for these jobs with a degree and skill that more closely matches the tasks they need to perform. For the biotech industry, that talent is increasingly available with Associate of Arts or Associate of Science degrees.

Close to 6 percent of the 1,655 community colleges in the U.S. offer either biotechnology certificates or associate degree programs. That number should double within the next five years barring substantial state budget cuts, which typically fund community colleges. These life sciences education courses can be completed relatively quickly. And they give A.A. and A.S. biotechnology candidates experience with crucial hands-on equipment and GMP training through certificate programs that provide the industry skills needed to perform critical tasks that traditionally have fallen to those with Bachelor of Science degrees.

A biotechnology certificate program carries few prerequisites and offers a broad introduction into biotechnology. Most programs consist of about 15 to 25 credit hours and may be taken in two to four full-time semesters.

The courses include basic concepts of biotechnology, current manufacturing practices, the molecular basis of carcinogenesis, food biotechnology, biological computation, drug design, and targeting. A biotechnology certificate or diploma paves the way to a job as a laboratory or research technician. Graduates are trained in microscopy, cell culturing, GMP documentation, autoclaving, basic microbiology, and environmental monitoring. Best of all, these graduates are highly motivated; the retention rate of A.A. graduates from biotechnology programs is two to three times higher than scientists from conventional bachelor's degree programs in biotechnology.

These students often are more mature or in their late 20s or early 30s and are looking for a different profession or career. They invest their own time and money in the effort. It's not uncommon to see someone with this type of training and background last five, 10, or even 15 years instead of turning over in two years, which is common for more highly degreed workers. These folks want to build careers, not just have jobs.

If you want to give your company the chance to retain talent, don't be afraid to look beyond habit-driven hiring practices and focus on needs-based models. Hiring from conventional undergraduate programs will never go out of style. But it may not always be your only path to achieving bottom-line success when it comes to acquiring the right people for the tasks at hand.

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The Best Way To Set Goals In The New Year

KEN BLANCHARD, PH.D.

KEN BLANCHARD, PH.D., is a sought-after author, speaker, and business consultant. His best-selling book, *The One Minute Manager*, coauthored with Spencer Johnson, has sold more than 17 million copies worldwide. He is cofounder, along with his wife, Margie, of The Ken Blanchard Companies, a global training and consulting firm.

It's no secret that all good performance starts with clear goals — and the beginning of the year is a great time to set those goals. But how many of you take the time to create clear, motivating goals with your staff?

I believe everyone has the potential to be a high performer; people just need to understand what they are being asked to do and what good performance looks like.

WHERE DO YOU WANT TO GO?

The children's story *Alice's Adventures In Wonderland* provides a perfect example of the importance of setting goals. When Alice asks the Cheshire Cat which path she should take, the Cheshire Cat responds, "That depends on where you want to go." When Alice says she doesn't know, the smiling cat says, "Then it doesn't matter." The same is true in the work environment. If people don't have a clear understanding of where their focus should be, they can't perform at their highest level.

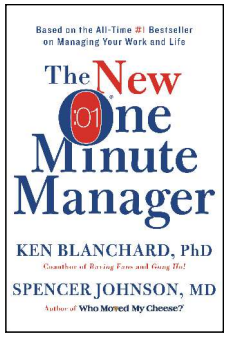
Long gone are the days when the manager established goals for employees and handed them over as a set of directives. Today, goal setting should be a collaborative activity that manager and direct report work on together, where they write a goal statement for each area of responsibility and include standards that will be used to evaluate performance. This provides clear direction on both what the direct report needs to accomplish and how they will know they have done a good job.

BEST PRACTICES FOR GOALS TO BE EFFECTIVE

The best practice is to write each goal on a separate page. Keep the goal statement short so that each day it will take less than a minute for the employee to review each goal to make sure they are on track. That's right — I'm suggesting that everyone look at their goals every day. Why? Because too often, goals are written and then put in a folder, not to be seen again until it's time for the annual performance review.

Creating goals and hiding them from sight for a year virtually guarantees that people won't work on the most important projects in an organized way. But when people read their goals every day, their behaviors are more likely to match their goals, they can adjust their actions if they are veering off track, and they are constantly reminded how their work contributes to larger department or organization initiatives. This method actually lets people manage their own performance, which in turn helps them enjoy their work more and be more productive.

The best minute of the day is the one you invest in people. The start of a new year is a perfect time to work together and set goals that will not only bring out the magnificence in people but also set your organization up for success.



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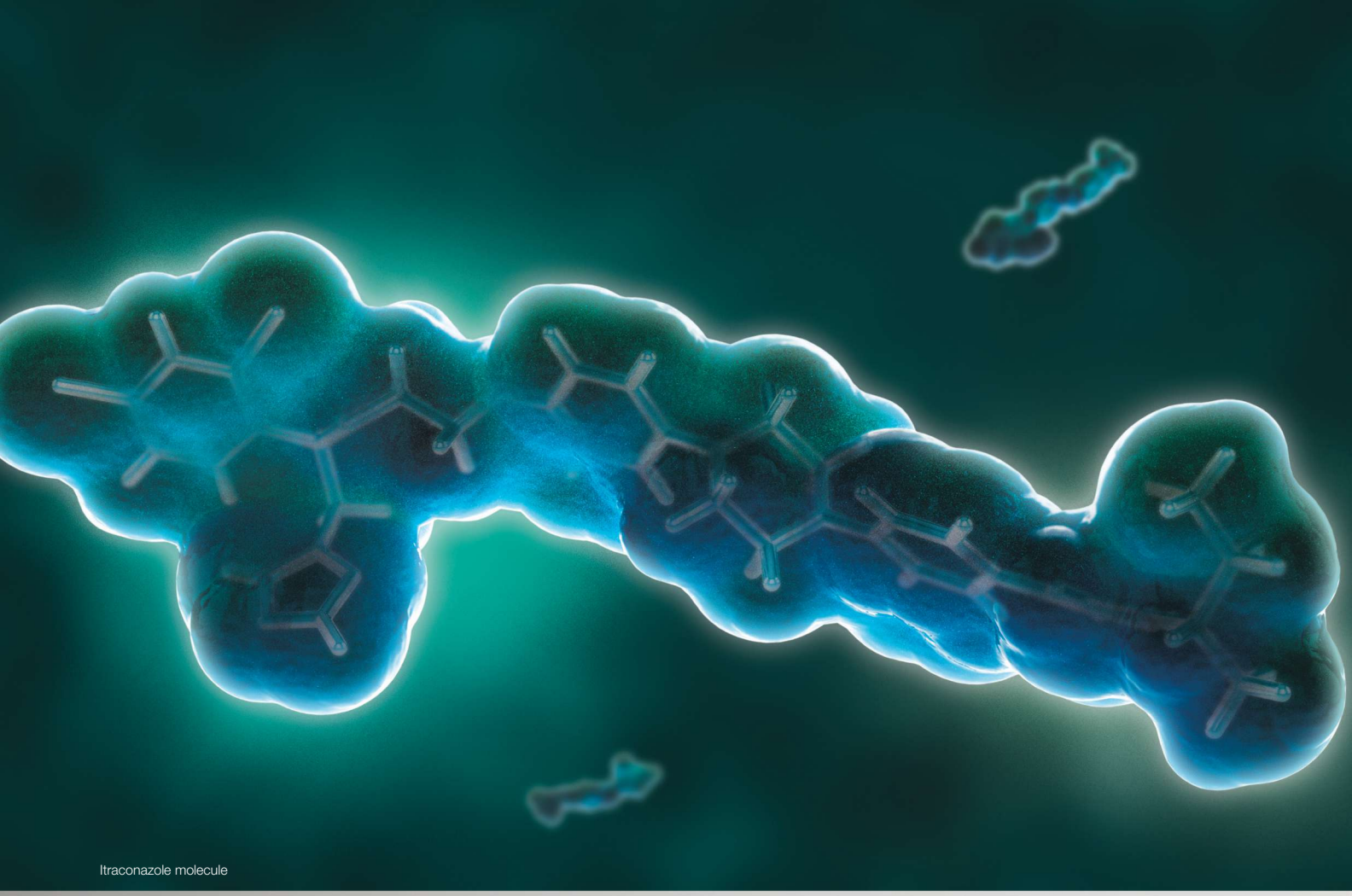

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