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LEADERSHIP

Innovation | Influence | Intuition

Biotech CEOs: Can Scientist Founders Remain In Charge?

Beyond The Watershed: Gene Therapy Investment And Promise

The Eye Travels Wide: ProQR's Bid For Leadership In Genetics Of Sight

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THE LEADERSHIP ISSUE

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DEPARTMENTS

EXCLUSIVE ONLINE CONTENT

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From The Editor

LUCIE ELLIS

Investors "are looking at you as an individual; how you think about your strategy, how you discuss and interact with them. They are constantly assessing the team you have built around you," one scientist-turned-CEO told *In Vivo*'s Melanie Senior. Their comments feature in a wider story focused on how and when biotech founders remain as leaders of a company, and – as is more often the case – the events that cause them to step aside.

There is a new breed of leadership in the life science sector, PhD-carrying entrepreneurs who want to personally help translate their ideas into the clinic. In this article, we explore the skills required to lead a biotech business from start-up to commercial triumph. There are several routes to success and founding members of a biotech company play different roles in the journey. Still, there are challenges when it comes to the talent pool for new and emerging leadership.

May's issue also includes exclusive interviews with Frank Mathias, CEO of Rentschler Biopharma, a contract development and manufacturing organization; Matteo Mantovani, CEO and technical director of NCS Lab srl, a certified research lab that engages in medtech lifecycle research, including design, testing and failure analysis; and Christophe Bancel, CEO of TISSIUM, a medtech company developing an innovative polymer aimed at tissue reconstruction.

Elsewhere, in a discussion piece by Jo Shorthouse, Janet Lambert, CEO of the Alliance for Regenerative Medicine, highlights commercial challenges still ahead for this sector even as R&D breakthroughs continue to emerge.

Finally, a different style of leadership; William Looney speaks to ProQR's founder and CEO Daniel de Boer about the company's R&D strategy and making difficult decisions. Now seven years old, and still awaiting its first marketed product, ProQR does meet the criteria for standout status in emerging biotech. It has had a visionary founder and CEO in de Boer, driven by his family's own exposure to incurable disease; a supportive cast of advisers from the "Dutch diaspora" of world-class, business-building talent, including the late, rare disease legend Henri Termeer; and an inclusive relationship with activist patient stakeholders.

Up-Front

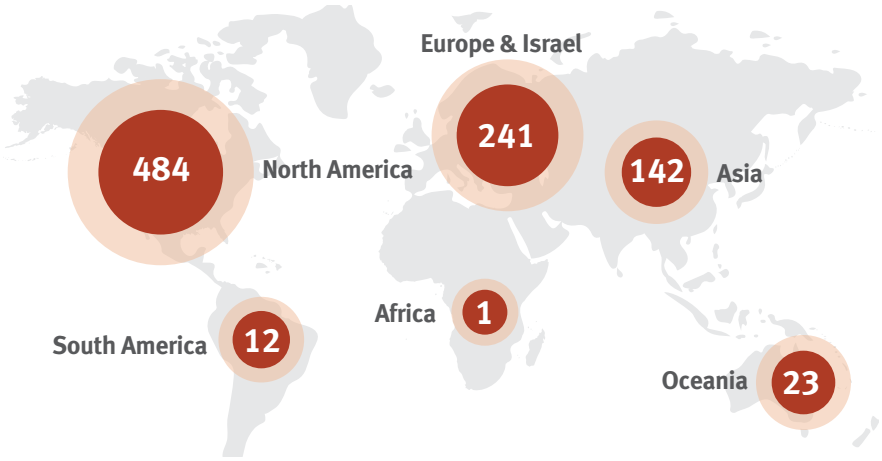
SNAPSHOTS FROM MAY'S CONTENT

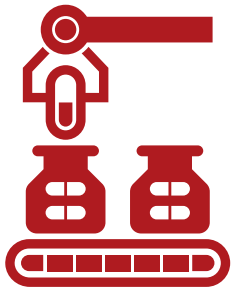
In today's biopharma, the eyes have it – and the search is on for ophthalmology companies with solid science and a strong, clinically differentiated message. One start-up with a direct line of sight to both is Dutch-based ProQR Therapeutics NV.

PAGE 30

There are more than 900 regenerative medicine companies worldwide. In 2018, companies active in gene and cell therapies and other regenerative medicines raised more than $13.3bn.

PAGE 16





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KEY FINDINGS

from Rentschler for CDMO evolution:

- quality will remain the main driver for success
- communication between clients and CDMOs needs to evolve
- the one-stop shop approach will remain favorable

PAGE 22

"My goal is to be the worst person in my company," says Arnon Rosenthal, serial founder and CEO.

"If someone can be a better CEO than me, I'll give them my job."

PAGE 10

There is a way to use failure investigation at an earlier stage in the design and development process to improve understanding of how devices fail to perform when out in the field, and thereby avoid potentially catastrophic effects.

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Around The Industry

New AdvaMed Chair Lobo: Devices Have A Good Story To Tell

CVRX CEO Nadim Yared will be a hard act to follow as AdvaMed chair, as his list of accomplishments over the past two years, as well as his ability to maintain the spotlight on the medtech industry in the US and beyond, have shown. In Kevin Lobo, CEO of Stryker Corp., the industry has a leader who will continue to push back the boundaries for SMEs, as well as developing his own agenda points.

Lobo's two-year tenure was announced on March 27, and he knows that the 2012 medical device excise tax will continue to throw a long shadow over the US industry as a whole and AdvaMed's relationship with lawmakers in particular until it is permanently repealed. At present, it is due to be reinstated at the end of this year.

Meanwhile, congressional efforts continue to be made to delete the tax, most recently in the form of the April 10 introduction in the House of Representatives the "Protect Medical Innovation Act of 2019 – another step towards a permanent repeal of a tax that AdvaMed said would cost industry $20bn if the current suspension ended. This threatens individual companies as well as America's traditional leadership of the industry, noted AdvaMed.

Thus, Lobo expects much of his chairship to be spent educating new members of Congress and highlighting how medical devices have accounted for less than 6% annually of US health care spending over the past 30 years. In 2016, that dipped to just 5.2%, and prices covered by Medicare are actually declining, Lobo told reporters, on both a nominal and inflation-adjusted basis. Prices for hip and knee replacements, for example, are trailing recent levels by 12% and 18%.

But Lobo, who came into the industry just 12 years ago, is ready for the challenge. "We've got a good story to tell," he said, referring to the value medtech delivers, even though it can tend to be overlooked in the wider health care economy debate. He also said his experience outside the industry would bring new ideas around "how we can advocate for the industry with all stakeholders."

"We need to attract the best talent from the minorities and women. This is an area we can do more in and is a priority for us."

Kevin Lobo
CEO of Stryker Corp.

Part of his challenge will be setting a dialog with a new FDA commissioner. In hindsight, Scott Gottlieb was like a meteor for change flying over US health care products regulation. He was another individual with apparently boundless energy for securing improvement. He did not quite have the time to burn out as he left fairly abruptly after 23 months of fast-paced activity, leaving medtech industry stakeholders somewhat bereft. On the plus side, Jeff Shuren at the CRDH has become a leader who medtechs increasingly trust and respect.

Lobo has been a member of the AdvaMed board since 2012, and served on its international committee between 2015 and 2017. *In Vivo's* sister publication *Medtech Insight* notes that he is also a board member of the influential business lobby group, the Business Roundtable, which comprises CEOs of leading US companies. The group collectively represent every sector of the economy and bring a unique perspective to bear on policy issues that impact the markets.

SUPPORT FOR INTERNATIONAL INDUSTRY

He is an international as well as domestic leader for the sector. For example, he sees the EU Medical Device Regulation (MDR) as a critical issue for the medtech industry and patients in Europe. He told *In Vivo*, "We are rapidly approaching the May 2020 deadline when nearly all medical devices must be evaluated according to the MDR." He noted that industry had invested heavily to be in compliance with the new requirements, but major worry remained. "Our concern is that the regulatory system will not be ready ahead of the deadline, which could disrupt patient access to medical technology."

In this sense, AdvaMed supports MedTech Europe's work to urge European institutions to take "appropriate measures" immediately to ensure continued access to existing life-saving and life-improving medical devices and diagnostics.

PATIENT ENGAGEMENT AND INNOVATION EFFORTS

He reiterated that devices had a great story to tell. "We haven't told our story as loudly as we should," he said, vowing to communicate more directly with stakeholders and do more patient engagement and outreach.

"One of my key priorities as chair will be to focus on the advancement of new

technologies – which includes advocacy efforts for the entire innovation ecosystem, including emerging growth companies." The priority is to secure predictable pathways to approval and reimbursement, said Lobo, taking the view that "we've done well with regulators, and now we want to do that with the CMS."

AdvaMed will be covering the entire ecosystem – including start-ups and SMEs. Lobo will continue the work of Yared, "a great advocate for this portion of the industry," which makes up about 70% of AdvaMed's membership. "Smaller companies are a vital part of the medtech ecosystem and the source of so much innovation."

DIVERSITY AND INCLUSION

Lobo has also chosen to focus strongly on diversity and inclusion in the industry. "We need to attract the best from the minorities and women. This is an area we can do more in and is a priority for us." He acknowledged that there were some concerns within the industry on US immigration policy, and how it could affect industry. AdvaMed's key initiative is improving diversity. "There's a lot of progress we can make here."

The association has also set up a women's executive group, and such initiatives are seen as "really exciting" by the new AdvaMed leader. "I really plan to dial this up during my time as chair," he said. In December, AdvaMed's board also formed the Board Inclusion and Diversity Committee to discuss and implement further initiatives to improve diversity.

IN 2021, THE CRYSTAL BALL SHOWS...

Two years hence, Lobo hopes to have secured solid progress in each of his priorities as chair. Specifically he wants to see progress for AdvaMed's engagement with the patient community and more work around ensuring members of Congress and other policy makers in the US and abroad have a better understanding of industry's key issues. He wants better messaging on how the medtech sector innovates and the "incredible benefits we bring to patients and health care professionals."

In addition, he wants to have increased the predictability, efficiency and transparency at the FDA and developed strong momentum in repeating that successful model at CMS. And finally, both catching the Zeitgeist and developing a new policy all of AdvaMed's own, he wants to have made "meaningful progress promoting and encouraging diversity and inclusion in the medtech industry."

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ASHLEY YEO

Israel Looks To Nurture New Leaders For Burgeoning Biotech Sector

Israel's life sciences sector is celebrated for its academic excellence and extensive basic R&D coming out of the likes of world-renowned establishments such as the Weizmann Institute and the Hebrew University of Jerusalem. There has historically been a lack of homegrown leadership to establish companies that can bridge the gap between discovery and getting products into late-stage trials, but this is changing.

Someone well-equipped to see how the sector is developing and how companies are being created is Anat Naschitz, a managing director at health care investment firm OrbiMed, which is currently investing out of its second Israel-focused $307m venture capital fund. While the country has a thriving medtech industry, and is known for its expertise in fields like cybersecurity, artificial intelligence, IT and smart phone technology, "historically, there wasn't that much biotech investment and as a result, there was also less biotech entrepreneurship, although there was a lot of innovation happening in academia," she told *In Vivo* in a recent interview.

That innovation was being licensed directly from universities to big pharma (*see Exhibit 1*) with not much in between. "There was no biotech industry *per se* here," said Naschitz, but OrbiMed, other investors, and crucially the government through the Israel Innovation Authority, have invigorated the sector. This has helped firms move from preclinical to clinical development and perhaps beyond. "We now see a vibrant biotech industry developing exciting science."

Naschitz cited the example of 89bio, which OrbiMed founded after acquiring a non-core asset from Teva, now called BIO89-100, which is currently in Phase I for nonalcoholic steatohepatitis (NASH). The drug is a long-acting glycopegylated fibroblast growth factor 21 (FGF21) analog and the company closed a $60m series A financing in October, led by OrbiMed, while Longitude Capital, RA Capital Management and Pontifax also participated.

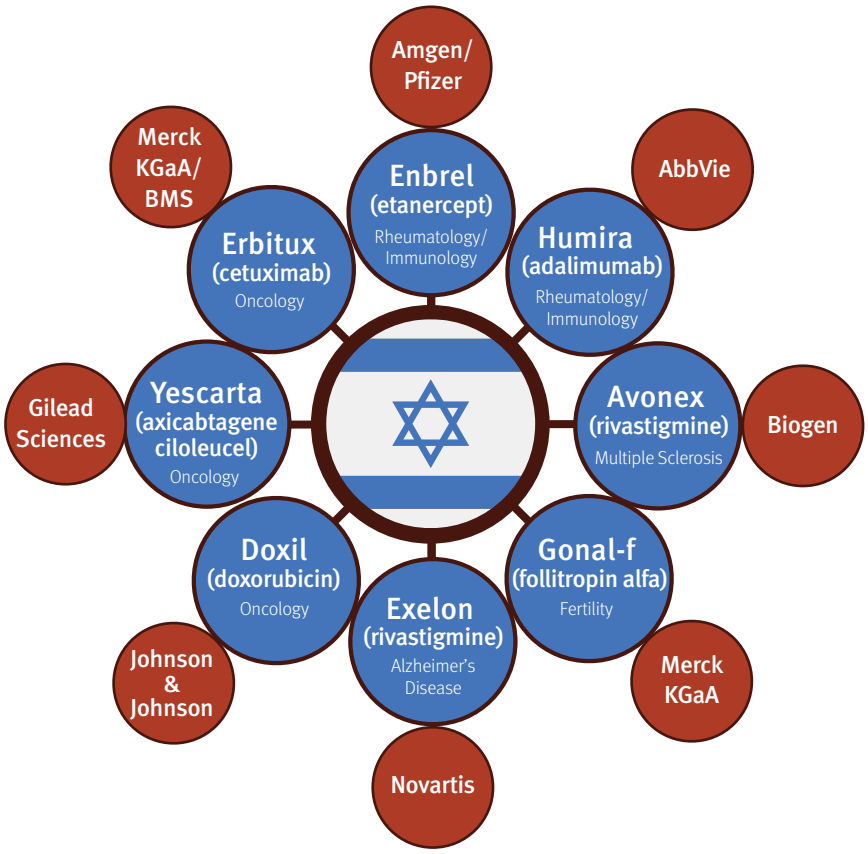
89bio, which is headquartered in San Francisco with R&D operations in Herzliya, Israel, has a drug with strong preclinical data behind it that came from big pharma and is being developed in the hot area of NASH. The therapeutic candidate has shown activity in both metabolic and fibrosis endpoints of the disease, Naschitz noted. Pointing out that FGF21 is a clinically validated target, she said BIO89-100 had demonstrated a long half-life in preclinical studies, potentially enabling extended-interval dosing, and it has already attracted some interest from companies focusing on NASH.

OrbiMed has helped to assemble a strong leadership team at 89bio "that can flex themselves along the way and adjust to what life has to offer," Naschitz said. "You want to see a team that represents very deep science and an ability to manage the trials and also interact with people who would want to ultimately buy it or take it public."

So does the biotech sector in Israel

Exhibit 1

Born In Israel, Developed Elsewhere



have the right people to bridge the gap between preclinical and the clinic? Naschitz is confident it has, "we do have excellent, smart people who are very tenacious and very strong and there is a developing cadre of people that do have that expertise. Some of them are homegrown and some of them are people who have been in big pharma or biotech companies abroad who either have returned here, or continue to work somewhere else, but are good partners for Israeli companies because they know how to work with them."

COMPUGEN'S AGENDA

An established Israeli company that has assembled a strong management team, an impressive scientific advisory board and signed up some major big pharma partners is Compugen Ltd. and its CEO Anat Cohen-Dayag has ambitious but realistic targets going forward.

"We are not a big pharma company that has deep pockets, so we need to build our path forward strategically and financially in the right way," she told *In Vivo*. Compugen has transitioned from being a firm with computational predictive discovery capabilities to one that in 2018 saw two clinical trials begin: COM701, a first-in-class antibody targeting a new immune checkpoint discovered by Compugen called *PVRIG;* and Bayer AG initiating a Phase I study for BAY 1905254, an anti-ILDR2 antibody, again computationally discovered by the Holon-headquartered group.

Last year also saw Compugen ink a couple of major deals. It linked up with Bristol-Myers Squibb Co. in October to evaluate COM701 in combination with the latter's PD-1 inhibitor Opdivo (nivolumab) in patients with advanced solid tumors, banking a $12m equity investment from the US major. In April 2018, a pact was signed with AstraZeneca PLC, through which the UK-headquartered pharma giant paid $10m upfront for a license to develop bispecific and multi-specific antibody products derived from Compugen's pipeline.

Cohen-Dayag noted that having reached "these important inflection points," Compugen has recently undertaken a strategic review designed to cut overlapping R&D and general administration activities in Israel and the US. This will result in a 35% workforce reduction (approximately 35 employees) and will bring in savings of up to $10m on an annual basis. Restructuring costs are expected to be in the range of $27m-$29m.

These measures should extend the company's cash runway through mid-2020 to enable the planned expansion of the ongoing Phase I study for COM701. "To be a robust biotech company, you need to be able to bring yourself to the industry standard and you need to learn it from someone," Cohen-Dayag said.

She added that "we're getting a lot of help from good advisors and we listened very carefully. Obviously, we make judgment calls on what we do internally but good advice is priceless, scientifically and strategically."

Compugen has got some heavyweight strategic advisors as well, such as Elliott Sigal, president of R&D for BMS from 2004 until 2013; and Steve Holtzman, CEO of hearing loss firm Decibel Therapeutics and former head of corporate development at Biogen. The scientific advisory board also includes some big names, such as Drew Pardoll at Johns Hopkins University of Medicine, the first person to propose blockade of PD-1 for cancer therapy, and Columbia University's Charles Drake, who specializes in immune checkpoints and cancer vaccines.

Cohen-Dayag is clearly all for collaboration and said it can only help the Israeli biotech ecosystem. "I think very highly of the innovation here and I'm very proud of it. I hope that a lot of this innovation will sustain Israel in order to grow and generate value. As an industry, we're trying to make efforts so this will happen on all fronts," she said, noting that there are more venture capital firms now, which means accessing money is less of a problem. Still, "we're trying to build more clinical expertise, industry expertise and managerial expertise," said added.

Her vision is to create value not only for Compugen shareholders, but also for the country as a whole "and to have more workplaces for Israeli employees. If we can lead it, that would be great."

ISRAEL BIOTECH FUND

Another industry veteran who is confident that Israel can create a sustainable pharma sector is David Sidransky, co-founder and general partner of Israel Biotech Fund. A renowned oncologist, he was vice-chair of ImClone until its acquisition by Eli Lilly for $6.5bn in 2008 and founded several biotechs, including Oncormed Pharmaceuticals and Response Genetics.

Sidransky moved from the US in 2010 to Israel where he saw lots of "opportunity and some of the limitations." He told *In Vivo* that the biotech sector was strong in terms of numbers of scientists, projects and startups, but there was a lack of knowledge "in terms of both realizing how much money it took to get going and how much money you needed to actually make it happen. Companies would start and they wouldn't have enough money to move through the process of drug development."

Another factor is that the main player by far in the Israeli health care sector is Teva Pharmaceutical Industries Ltd., which is predominately a generics firm. The company has not “quite managed to get themselves on the innovative bandwagon,” Sidransky said. "Entrepreneurship coupled with regulatory clinical knowledge needed for innovative new drug candidates” is still missing from the market, he noted. “When we started the fund we realized that, in addition to the people on the ground, we needed a much larger group of experts from industry."

The team of advisors gathered by Sidransky and his colleagues at IBF reads like a who's who in the pharma industry. They include Sol Barer, founder of Celgene Corp. and chair of Teva; ex-Pfizer Inc. CEO Jeff Kindler; Bob Spiegel, former chief medical officer at Schering-Plough; and Murray Goldberg, ex-CFO of Regeneron. The 35-strong group of advisors meet once a month.

> “Entrepreneurship coupled with regulatory and clinical knowledge needed for innovative new drug candidates is still missing from the market. When we started the fund we realized that, in addition to the people on the ground, we needed a much larger group of experts from industry.”
>
> **David Sidransky**

As investors in the IBF, "they have skin in the game and they commit a tremendous amount of time both evaluating companies, helping devise strategy, recruiting the right people, and importantly, sitting on boards – which is crucial so that we can manage and help the portfolio company,” Sidransky said. The fund has a number of success stories on its books including Ayala Pharmaceuticals, which is developing gamma secretase inhibitors licensed from BMS and stem cell specialist Gamida Cell Ltd., which listed on the Nasdaq in October last year.

(Also see "Israeli Startup Ayala Taking BMS Cancer Drug Into Phase II With $17m Financing" - Scrip, 10 Apr, 2018.)

"All of our investors are in it for the long run and our vision is that we want to further build the industry in Israel," Sidransky said, noting that quick exits "enrich the first few investors but they don't enrich the ecosystem and we want to grow a very big footprint here." He added that the goal is to develop two or three large innovative companies, creating sustainable jobs for Israelis right across the development pathway. Ruti Alon, CEO of venture capital fund Medstrada and co-chair of the MIXiii-BIOMED conference (see below) noted that as the sector has matured, there are indeed a number of biopharma companies developing drugs in clinical and even late stages in a variety of areas, citing the likes of UroGen Pharma, VBL Therapeutics, Anchiano Therapeutics, Pluristem and BioLineRx. Their advancement is due in part to "the Nasdaq opening its doors to Israeli biotechs and the financial boost that the life science ecosystem received with the addition of new VCs in the healthcare space," with aMoon and the IBF joining firms such as OrbiMed, Pontifax, Arkin Bio Ventures and Clal Biotechnology Industries.

"I believe that this positive momentum can eventually create a sustainable and leading life science industry in Israel," Alon concluded.

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KEVIN GROGAN

Naschitz and Sidransky co-chaired, respectively, the AI/Digital Health and Transformative Cancer Therapies tracks at MIXiii-BIOMED, Israel’s leading international life science conference and exhibition, held May 14-16 in Tel Aviv.

2019 TITANS OF PHARMA

	CEO				
		ALEX GORSKY	IAN READ/ ALBERT BOURLA[3]	SEVERIN SCHWAN	VASANT NARASIMHAN
					
	COMPANY	JOHNSON & JOHNSON	PFIZER	ROCHE	NOVARTIS
		US	US	SWITZERLAND	SWITZERLAND
Appointment Date		2012	2010	2008	2018
Previous Position		Chair, J&J Medical Devices	Pfizer SVP, group president, Worldwide Biopharmaceuticals	CEO, Roche Diagnostics	Global head of drug development and chief medical officer, Novartis
Background		Began career as sales rep at Janssen Pharmaceutica, J&J. Defected to Novartis as head of pharma for North America 2004-2008 before returning.	Career spent at Pfizer, joined as an auditor. Has chemical engineering and accounting qualifications.	Economics, law degrees, joined Roche as trainee in corporate finance in 1993.	Medical degree, master's in public policy. Joined Novartis in 2005 after working at McKinsey & Company.
Compensation[1]		$20.1m (-32.6%)	$19.5m (-30.0%)	CHF11.8m (+0.6%)	CHF9.9m[4]
Median Employee Compensation[2]		$75,000 (268:1)	$80,011 (244:1)	n/a	n/a
Company Sales		$81.6bn	$53.6bn	CHF56.8bn	$51.9bn
Company Net Profit		$15.3bn	$11.2bn	CHF10.9bn	$12.6bn
Market Cap		$376.2bn	$227.7bn	CHF234.8bn	CHF240.4bn
R&D Head		Paul Stoffels	Mikael Dolsten	n/a no single R&D chief	John Tsai[5]
Appointment Date		2009	2010	n/a	2018
Previous Position		Worldwide chairman, Pharmaceuticals (J&J)	Head of Wyeth R&D, previously at Boehringer Ingelheim and AstraZeneca	n/a	Chief medical officer, SVP of global medical, Amgen
Compensation[1]		$10.6m (-22.0%)	$7.1m (-7.8%)	n/a	CHF5.9m[6]

[1] Base salary, bonus & long-term incentives (including equity awards)

[2] Ratio of CEO compensation to median-paid employee 2018

[3] Albert Bourla on 1 Jan 2019 replaced Read. Compensation figure for Ian Read is displayed

[4] Assumed role on 1 Feb 2018; Joseph Jimenez was CEO until 31 Jan 2018 and received CHF2.7m

[5] From 1 May 2018

[6] Started role in 2018; Vas Narasimhan received CHF4.5m in the R&D role in 2017

A snapshot of the industry's top leaders and the businesses they oversee

	WERNER BAUMANN	KENNETH FRAZIER	EMMA WALMSLEY	OLIVIER BRANDICOURT	RICHARD GONZALEZ	DAVID RICKS
						
	BAYER	MERCK & CO	GLAXOSMITH-KLINE	SANOFI	ABBVIE	ELI LILLY
	GERMANY	US	UK	FRANCE	US	US
	2016	2011	2017	2015	2013 *(at company inception)*	2017
	Chief strategy officer & portfolio officer, head of EMEA, and head of Bayer HealthCare	President, Merck & Co, Inc	CEO, GSK Consumer Healthcare	CEO, Bayer HealthCare	Head of Pharmaceutical Products Group at Abbott Laboratories	President, Lilly Bio-Medicines
	Spent career at Bayer after studying economics.	Legal: joined Merck in 1992 as general counsel.	Before joining GSK in 2010 was with L'Oréal for 17 years in marketing and general management.	Physician by training, had leadership roles at Pfizer before Bayer.	Spent 30 years at Abbott.	20 years at Lilly. Marketing & sales, general manager roles after gaining bachelor of science and MBA.
	€5.3m (-17.1%)	$20.9m (+18.7%)	£5.9m (+70.3%)	€7.3m (-25.4%)	$21.3m (-6.0%)	$17.2m (+8.7%)
	€104,336[7] (51:1)	$91,954 (228:1)	n/a	n/a	$148,823 (143:1)	$91,246 (189:1)
	€39.6bn	$42.3bn	£30.8bn	€34.5bn	$32.8bn	$24.6bn
	€1.7bn	$6.2bn	£4.0bn	€4.4bn	$5.7bn	$3.2bn
	€57.8bn	$205.4bn	£77.4bn	€97.1bn	$116.0bn	$115.0bn
	Kemal Malik	**Roger Perlmutter**	**Hal Barron[8]**	**John Reed[10]**	**Michael Severino**	**Daniel Skovronsky**
	2007	2013	2018	2018	2014	2018
	Head of global medical development	Head of R&D, Amgen	President, R&D at Calico	Global head of Roche Pharma Research & Early Development	SVP, global development and corporate chief medical officer, Amgen	SVP, clinical and product development
	€2.6m (-14.4%)	$7.1m (+4.0%)	$6.6m[9]	n/a	$8.6m (+2.5%)	$5.1m[11]

[7] For employees based in Germany

[8] Patrick Vallance left the company on 31 March 2018

[9] Patrick Vallance received £4.4m from 1 Jan - 31 March 2018

[10] From 1 July 2018; Elias Zerhouni held the position until 30 June 2018

[11] Jan Lundberg was in the post in 2017 and received $7.4m

Biotech CEOs: Can Scientist Founders Remain In Charge?

Composition: KennyK.com and Janet Haniak

Founder-CEOs do not typically remain at the helm as biotechs mature. Exceptions to that rule are multiplying, though, especially in Europe as companies aim directly for Nasdaq.

BY MELANIE SENIOR

Most companies start out with a scientist in charge, often a scientist-co-founder. But he or she will typically lack the skills (and sometimes the will) to lead a company beyond discovery or early development.

Moving a scientist-founder aside can be challenging, both for investors and leaders. But there are exceptions - founders that do carry their companies to later-stage success. What are the skills required?

In Vivo reviews the many, varied paths toward the biotech CEO position, and the talents that all leaders need, regardless of their background.

There are several high-profile examples of biotech leaders who have seeded, nurtured and grown their companies into profitable, sustainable organisations. Josh Boger founded Vertex Pharmaceuticals Inc. in 1989 and was CEO for twenty years, building a $43bn behemoth. Jean-Paul Clozel, with wife Martine and two co-founders, built Actelion Pharmaceuticals Ltd. into Europe's largest, most successful biotech, finally succumbing to a $30bn offer from Johnson & Johnson in 2017. Art Levinson – not a founder, but a very early employee at Genentech Inc. – was promoted from R&D chief to CEO in 1995, defying skeptics to build the industry leader. The message from these success stories: science rules, not just at the start, but all the way.

These individuals are exceptional, however. Few combine the broad skill set (and dogged perseverance) required to discover and fund a scientific innovation, as well as turn it into clinical and commercial reality. Most companies start out with a scientist in charge, often a scientist-co-founder. But he or she will typically lack the know-how (and sometimes the will) to lead a company beyond discovery or early development. So once technological proof of concept is established, many investors will seek a CEO with more experience selling ideas to investors, including potential partners. Leadership transition becomes necessary.

"Often it is not ideal, or appropriate, for the founder-inventor to be the company's CEO," said Jonathan Tobin, investment director at London-based Arix Bioscience. In the case of high-profile academic founders like Nobel-Prize-winning Sir Gregory Winter, there is no issue: they would not want to leave their academic post anyway. Their technology or discovery forms the kernel of a commercial venture and they become members of the scientific advisory board.

But there is another breed of scientist-founder: PhD-carrying entrepreneurs who want to personally help translate their ideas into the clinic. This group is hugely valuable for getting ideas off the ground when it's all about the science. But few are equipped to lead a company beyond discovery. "The tough part is when you transition into development," said Morten Dossing, partner at Novo Seeds, which, like many other early-stage VCs, creates companies as well as investing in them.

Entering the clinic drives up costs and risks. The company's needs move beyond managing science, toward managing a growing palette of investors, and wooing the next round of cross-over or even public backers. For that, a leader must be sufficiently versed in finance to be able to assuage investors' concerns, and know "how to ask the right questions, and hire the right people," said Dossing. Such skills can be learnt. But an experienced CEO with an existing investor network will often be able move a lot faster and more efficiently. Founder-CEOs taken out of their comfort zones can often mean R&D "timelines begin to slip, and experiments are no longer conducted properly," warned one European-based investor. "Quality assurance can be a problem."

From the other side of the fence, scientist-CEOs feel the heat of investor scrutiny, especially as larger funding rounds accumulate. Investors begin to question "are you the one to deliver a good exit strategy?" said one scientist-CEO. "You could get your job curtailed quite fast if they don't think you're the person for the job," said Niall Martin, scientist-CEO of Cambridge, UK-based DNA damage repair response company Artios Pharma Ltd., and previously a co-founder and interim CEO of Mission Therapeutics.

The transition from founder-CEO can happen smoothly. There are dozens of examples of CEOs moving fuss-free, and often with some relief, to a chief scientific officer (CSO) position, allowing a more experienced chief executive to take over. The key is managing expectations, and tempering egos. If the founders know that "this moment is bound to happen," there is no problem, said Antoine Papiernik, managing partner at Paris-based VC Sofinnova Partners. Even in cases where leaders leave the company entirely, if the parties can discuss sensibly and put the company's fortunes ahead of their own, "it needn't be a trauma."

Some incumbent scientist-CEOs appear to agree. "It's more important that the company succeeds, than that I keep my chair," said Thomas Pedersen, co-founder and CEO of NMD Pharma AS. "I want this [company] to be the kind of place where we can have the conversation [about who is best for the role] and figure out the way forward. I want to be self-aware," said Emmanuel Simons, co-founder and CEO of Boston-based gene therapy company Akouos.

Misaligned Interests

Still, there are plenty of cases where "you may need to extract management with a chainsaw," admitted another investor. These situations tend to arise when a lethargic board has waited too long, letting a bad situation worsen. Each case is unique, but scientist-CEOs may be more likely to want to run a wider range of experiments, lacking focus. They may also have a deep personal attachment to the technology or approach, clouding judgment of its clinical applicability. Many investors, on the other hand, are singularly and objectively focused on the next inflection point: a data read-out that triggers another funding round (at a higher valuation), a lucrative partnership, or a sale.

The interests and the vision of CEOs – especially founder-CEOs - often diverge from those of the board and shareholders, even when the founder does step aside into a CSO or alternative role. Such misalignments arise in "over 50% of cases," according to one prolific investor (though they needn't always lead to the CEO's departure). Given how biotechs are built and funded, in most cases "a founder-CEO quickly loses control of the company," said serial founder and CEO Arnon Rosenthal, currently heading up San Francisco-based immuno-neurology company Alector. Founders' ownership percentages typically fall into low single-digits once significant funds have been raised. That means "the only control you have is your ability to convince investors that you can add value," said Rosenthal, who previously co-founded and ran Annexon Bio, and also co-founded and was CSO at Rinat Neuroscience, sold to Pfizer in 2006. (Another recurring point of tension between management and board is whether and at what stage to sell out. (*See Box: To Sell or Not to Sell.*)

TO SELL OR NOT TO SELL?

Actelion's Clozel (who became CEO after the company's 2000 IPO) convinced his shareholders to resist multiple takeover offers over the course of Actelion's evolution, including when facing additional pressure from activists. Edwin Moses, ex-CEO of Ablynx, said several board members resigned as the company turned down an initial low-ball acquisition offer from Novo Nordisk. It is not just about opinions; liabilities and fiduciary duties are at stake for board members representing the interests of a broader shareholder base.

For many private investors, "adding value" means generating tangible progress that enables a profitable exit. That in turn means carefully allocating limited existing funds, perhaps focusing on just one or two programs. Yet "very few scientist-CEOs that I have seen are sufficiently focused on that [capital allocation]," reflected one early-stage investor. "Many lack the skill-set to run a capital-hungry company."

Assembling CEO Skills: Teamwork And Humility

They can learn those skills, though, just like non-scientists do. Indeed, "I think the finance is easier to pick up [for a scientist] than the science would be for a finance guy," noted NMD's Pedersen. A physiologist and associate professor at Aarhus University, Pedersen created NMD to turn his discovery of a new way to strengthen communication between nerve and muscle fibres into new treatments for neuromuscular disorders. During these early days – NMD raised a series A in 2018 – having a scientist at the helm is vital. "We have intense scientific debates...and I'm well prepared for that."

Learning to build and manage a team is a key skill for any aspiring manager, scientist or otherwise. As that team is

built, one of the hardest yet most important parts for a scientist-CEO is "giving up the science, as it's your natural home," admitted Artios' Martin, who initially served as both CSO and CEO. Pedersen agreed that letting go of the detail in the science is difficult, but necessary. "You have to trust your team," he said, adding that "they [the R&D team] are now probably better than me anyway."

Humility is another required trait for emerging CEOs – alongside confident leadership. "You need to be honest about what you don't know, and build a team around you that can support you in your weaker areas," said Pedersen. Rosenthal goes further. "My goal is to be the worst person in my company," he said. "If someone can be a better CEO than me, I'll give them my job."

As for resource allocation and managing investors, "it's challenging," acknowledged one first-time CEO. "We were criticised at one stage for looking at too many projects." What's important, he said, is to have a clear clinical line of sight. And tell investors the truth, "especially when things are likely to take longer than they expect."

Scientist-CEOs are clearly learning fast: Alector pulled off a $176m Nasdaq IPO in February 2019. NMD raised €38m ($47m) in 2018. Artios brought in a £65m series B in late 2018 – 30% more than it had set out to raise.

Staying In The Driving Seat

But no one is getting too comfortable. These CEOs know they may be moved aside as their companies progress. All face a constant battle to prove to investors that they are the right person for the job – not just delivering the science, but spotting and executing the next big deal or IPO. "They are looking at you as an individual; how you think about your strategy, how you discuss and interact with them. They are constantly assessing the team you have built around you," said one scientist-CEO.

Having longer-term investors may extend scientist-CEOs' time in the driving seat. Local backers in some parts of Europe are driven, at least in part, to help build a biotech ecosystem and support new talent. Even in the US, some entrepreneurs may be in a position to select patient investors that may offer the company a longer runway. Rosenthal did during Alector's early stages, and first-time CEO Simons, too, had the luxury of choice thanks to working in a red-hot field (gene therapy for the ear) with high-profile scientific co-founders and a top-notch network.

Some scientist-CEOs will remain primarily scientists, even as they manage a company through a public listing and beyond. (*See Box: A Personal Vision.*) Some will return to the science, while others will transition to become more conventional leaders. There are no hard and fast rules; "you have to sense" an individual's potential, taking into account the surrounding circumstances – the science, the characters, the investors, said Christian Schetter, entrepreneur-in-residence at Arix Bioscience, which builds and invests in biotech companies. Schetter was previously CEO of Neovii Biotech and Rigontec (acquired by MSD) and an SVP at Coley Pharmaceuticals prior to its acquisition by Pfizer.

Direct-To-Nasdaq Builds Europe's CEO Talent

In Europe, most biotechs are acquired before getting much beyond mid-stage development. Europe's risk-averse public markets – relative to the US - mean few groups are able to raise the funds they need for Phase III trials. The result: few European biotech CEOs get the chance to experience an IPO, compounding an existing talent shortage.

Going public is not the obvious job for scientist-founder CEOs, especially those seeking to keep their noses in the lab. An IPO involves months-long investor road shows. The science is important; the investment proposition more so.

Yet plenty of US scientist-leaders have done IPOs, given more generous and dynamic public markets that are prepared to support companies at an earlier stage. Harren Jhoti co-founded Cambridge, UK-based Astex in 1999, becoming CSO then CEO. The company was acquired by Otsuka Pharmaceuticals in 2013 and today operates as a wholly owned subsidiary with Jhoti as president and CEO. He noted that, if Astex had been in the US, the company would have listed several years earlier, in 2005/2006. "We may then have become a more commercially-focused, with a stronger drive to take one of our internal products to market ourselves rather than establish partnerships with pharma," Jhoti said.

Europe's dispersed biotech hubs and different languages and cultures present another challenge to building the local CEO talent-pool, since top executives cannot always be found (or be willing to move) near the sites of company-creation. In sum, although the region "has more capable CEOs than 15 years ago, the quality and quantity is still an issue," said Sofinnova's Papiernik.

As more European companies list directly on Nasdaq, that might change. "The only way forward for European biotechs is to go to the US," said Edwin Moses, who, as CEO of Ablynx oversaw both a local Belgian listing in 2007 and, ten years later, a US IPO. "We realized we were failing to get properly valued" in Europe, he recalled. Armed with Phase III data, the company raised $230m on Nasdaq, before selling out to Sanofi for $4.8bn the following year.

Next-generation CAR-T cell therapy company Autolus, founded in 2014 as a spin-out of University College London, did not even bother to list at home. The London-headquartered group raised

A PERSONAL VISION

Alector CEO Arnon Rosenthal views CEO-ship not as an end in itself, but as the most efficient means by which he can realise his vision of developing new drugs for degenerative brain disorders (underpinned by personally-discovered science). For Rosenthal, talking with investors and other business activities are "distractions" – though he acknowledges their importance. The CEO title does "significant damage to the science," he reflected – especially during an IPO. But how else to fund clinical programs in very expensive indications like Alzheimer's? Apart from the money, an IPO also represents "a reality check," Rosenthal said. "How competitive are we really?" Alector's shares are up 30% since listing.

$150m in a Nasdaq IPO in 2018, with assets still in early development. So did UK gene-therapy company NightStar Therapeutics (now being acquired by Biogen). Autolus is run by Christian Itin, who saw the benefits of a US listing back in 2006 as CEO of German antibody company Micromet. He reverse-merged with listed CancerVax in order to access US investors and facilitate follow-on funding. Micromet was acquired by Amgen in 2012.

Scientist-founder CEOs with a track record of making their investors money are more likely to be let loose with an IPO. Ernest Loumaye, co-founder and CEO of reproductive health company ObsEva, listed his Swiss-based group on Nasdaq in 2017, a year before a local IPO. Loumaye, a gynaecologist and professor of reproductive endocrinology, had partial experience of a US IPO with his first company, PregLem, co-founded in 2006. Loumaye was preparing to take PregLem public in 2010, "we had all the documents ready, the due diligence was done, and the lawyers were on hand." Then Gedeon Richter offered to buy the group, making some investors over six times their money in three years.

ObsEva was seeking US money to fund the launch of lead asset nolasibam, in Phase III trials as a treatment to boost IVF success rates. US investors' attitudes to this kind of regulatory and commercial risk contrast starkly with many of those in Europe, remarks one CEO. "The US financiers will ask, 'Are you sure you have a large enough sales force?' while the Europeans are worried about how quickly you can dismantle the sales force you do have, in order to minimise losses if the product fails."

Plenty of aspiring scientist-CEOs want to – and likely will – join this expanding pool of IPO-experienced European leaders. But sometimes European private investors want a leader already familiar with, and connected within, the investment world. David Solomon had been running healthcare investments at an early-stage venture capitalist in New York before taking over as CEO of Denmark's Zealand Pharma in 2008, replacing scientist-founder CEO Professor Eva Steiness. Free from the shackles of a founder's vision, Solomon carried out what investors wanted: more non-dilutive partnership funding from over half a dozen collaborators, and a local IPO to help build the in-house pipeline (a first IPO attempt in late 2004 had failed). By the time the company listed on Nasdaq in 2017, Zealand's board had appointed another, more commercially-focused CEO to oversee the company's maturing assets.

Solomon has a US IPO in his sights as CEO of UK-based Silence Therapeutics, working in the fast-evolving field of RNA interference. He's seeking to revive the fortunes of this 25-year old company whose UK-listed share-price, and pipeline, lag behind those of leading US RNA players like Alynlam Pharmaceuticals.

From an investor point view, "having done [a Nasdaq IPO] before is clearly a plus" in choosing a CEO, said Sofinnova's Papiernik. But, he continued, "it is not about the process. Anybody can do that. It is about knowing the public investors and having their trust before you even start." Solomon, like many other European biotech CEOs, spends a week a month in the US building share-of-voice with future investors. "I'm telling the story over and over, so that when it's time for a transaction, we'll have that support base," he said. "The most important thing as a CEO is to go there again and again. There is no substitute for shoe leather."

CHAIR-CEO: TWO IS BETTER THAN ONE

One of a CEO's most important relationships is with the board of directors. Boards – representing shareholders – hire CEOs to run the company on their behalf. The chair of the board can help a CEO to align investors and keep them on-side. A chair can flag up differences of opinion before they develop into damaging disagreements. He or she will help ensure board members are appraised of a CEO's plans before formal meetings, and may gauge each member's reaction to those plans as they are presented. "If you had to do all that as CEO, you would be overwhelmed," said Arix's Christian Schetter.

A good chair also brings to a CEO complementary skills, experience and an expanded network. This is especially important for first-time CEOs, including scientist-CEOs. "The chair and CEO fill each others' gaps," summed up SV Health Investors' managing partner Kate Bingham. She cited "heavyweight" chair Pierre Legault at Artios as a key ally to first-time CEO Niall Martin.

In some biotechs, particularly in the US, the CEO and chair may be the same person. Many European investors and executives see this as bad practice; in some markets like Germany and the Netherlands, governance laws do not allow it. Combining the roles may make for faster decision-making in a company's early days, but later on, too much power residing with one individual could raise governance issues. Some companies with combined chair-CEO positions, like UK-headquartered, US-listed Autolus, have standing committees and charters to meet governance requirements. But "they are different roles, so separating them is a tremendous advantage," opined Arix's Schetter. An independent chair can also provide a check on a leader's strategy: activist investors in troubled Allergan, seeking change, recently tried to wrench away the chair role from CEO Brent Saunders. They failed a first attempt, but Saunders agreed to split the roles – when the next CEO joins. The story rolls on, though; as *In Vivo* went to press, all options appeared to be back on the table.

Moses was chair and CEO of Ablynx until the roles were split in 2013, after Pfizer returned a key asset and shares plummeted. Although opposed to the timing of the move, which he felt showed a lack of confidence in management, "in the end, splitting the jobs was the best thing we did," he said. "It was much easier to do the CEO job" thereafter.

HONEST CEOS ON...

THE JOB

"The hardest part is to stay focused despite uncertainty. To convince people, internally and externally, that the risk is rational and that diversification often increases rather than decreases risk."

– **ARNON ROSENTHAL,** CEO and founder, Alector Therapeutics

"Give your staff ambition and confidence. Don't try to pull the wool over their eyes."

– **EDWIN MOSES,** ex-CEO, Ablynx

GOING PUBLIC

"Going public makes you grow up. It brings a formality. You need to be more rigorous – in both internal and external communication."

– **ARNON ROSENTHAL,** CEO and founder, Alector Therapeutics

EGOS

Once you are in the job, "it's important to put aside your ego and kill things early. Don't invest your time, your money or other people's money in anything that's not viable; in a project that has become an extension of you. If you're too connected to an idea, you are not going to be flexible enough as outside circumstances change."

– **DAPHNE ZOHAR,** founder and CEO, PureTech Health

Being asked to be CEO is a thrill and an honor. But it's important to "do your diligence carefully. Find out who is in control of the company. What are the issues? What do the shareholder(s) want? What are their constraints? Will they pull in the same direction?"

– **DAVID SOLOMON,** CEO, Silence Therapeutics

It's Lonely At The Top

All CEOs need a strong team around them. Each CEO may perform slightly different tasks based on his or her competencies. This does not matter, "as long as all the important functions are covered and people work well together," commented Sander Slootweg, managing partner at VC firm Forbion. He cited the example of oncolytic virus company Replimune, run by scientist-co-founder Robert Coffin (also founder and Chief Technology Officer of BioVex, sold to Amgen in 2011). Investors were comfortable with Coffin as CEO, knowing that former investment banker and BioVex CEO Philip Astley-Sparke was at his side as executive chair. "They [Coffin and Astley-Sparke] worked well as a team. They knew each other's strengths." Replimune raised $100m on Nasdaq in 2018.

Yet even amid a tight-knit team, being a CEO can be a lonely job. Whatever your background, "everyone wants to tell you you're doing it wrong," said one CEO. "You have to be able to go into a dark room, reflect upon your decisions and then have the confidence" to follow them through, whatever others are saying. "It's no good flipping on what this or that [individual] board member says," he continued, though if the whole board questions you, you may have a problem. A good chair can help avoid that situation. (*See Box: Chair-CEO: Two is Better Than One.)*

CEOs have the power to make things happen. That is what draws people to the top-job. Yet CEO-ship also means remaining outwardly confident amid near-constant uncertainty and challenge, and being comfortable addressing a wide range of issues, often concurrently. "You have to be able to hold lots of balls in the air, and enjoy the feeling of doing so," said Nikolaj Sorensen, CEO of Stockholm-listed specialty pharma firm Orexo AB. The buck stops with the CEO, who is under pressure to lead, and to manage the priorities of, employees, the board, and shareholders. As for being a CEO more than once, notes one serial scientist-entrepreneur: "it takes a certain kind of insanity."

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Comments:
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THE MANY PATHS TO BIOTECH CEO

There is no single path toward becoming a CEO. The job requires many different skills, often concurrently: sharp analytical capabilities, strategic thinking, clear communication with multiple audiences, curiosity and perseverance. It demands strong leadership but also humility, and a willingness to acknowledge mistakes and knowledge gaps.

CEOs emerge from a variety of backgrounds. In biotech, science training is clearly very helpful. But for later-stage companies – in development and beyond – a science degree or PhD is not necessary. Being too involved in the science can even be a disadvantage. What is important for the top-job in biotech, according to CEO-turned-investor Christian Schetter, entrepreneur-in-residence at Arix Bioscience, is having experienced "lots of different kinds of challenge across your career." Whether these challenges were in development, manufacturing, marketing or IT, what matters is appreciating the significance of each, and learning from them.

"You don't need to be experienced in everything. You just need to know enough to ask dangerous, critical questions; to be the one who can step out of, and see across, specific business functions and areas of expertise," Schetter said. You also need to adjust to the situation in hand. Each company will face particular technology-, market- and/or investor-related challenges.

LAW AND ECONOMICS: Nikolaj Sorensen, CEO And President Of Orexo

"I'm an economist with a law degree," said Sorensen. That law degree would become far more relevant than he'd "hoped or dreamed" as he took over the helm at Orexo AB in 2013. Orexo markets Zubsolv (buprenorphine and naloxone), used to treat dependence on opioid drugs like heroin and oxycodone. The field is competitive and politically sensitive too, given the US opioid ad-

diction crisis. One of Sorensen's first tasks as CEO was dealing with defeat in a patent dispute with generics firm Actavis. Another was managing a divorce from Orexo's European commercial partner, Mundipharma, which decided for strategic and PR reasons to exit opioid dependence treatment.

"CEOs are the last resort [to settle partner disputes] before arbitration," said Sorensen, who had previously worked at consulting firm BCG and as managing director of Sweden for Pfizer. As such, understanding the content of contracts, and some of the principles of law, "is a relatively big part of the CEO job." Unlike functional experts, CEOs don't get asked only about marketing, development, or commercial issues. They have to address all of them – and most involve a legal aspect.

SALES: Edwin Moses, Ex-CEO Of Ablynx

For Edwin Moses, who ran Nanobody company Ablynx for 12 years, a training in sales was a great preparation for being CEO – where the job "is selling the company and the idea behind the company," he reflected. Moses had a PhD and Postdoc when he started out selling high-value reagents to scientists. "The principles are very transferable," he said – taking great science and working out how to extract commercial value from it. After gaining exposure to shareholders and the investment world through working alongside the CEO at Italy's Raggio Italgene, he joined tiny chemistry services company Oxford Asymmetry as CEO. "You never know what you need. You feel under-prepared," when taking the top job for the first time. And Oxford Asymmetry, which became profitable, provided vital training in "paying proper attention to costs and margins," added Moses – an experience that those coming up through traditional loss-making biotechs may miss. Understanding the importance of cash, and the various sources of cash, would prove key during Moses' tenure at Ablynx, which raised over $1bn from investors and partners before its sale to Sanofi.

FINANCE: Biresh Roy, CEO Of Ascension Healthcare

Biresh Roy, CEO of Ascension Healthcare, knows about P&Ls. He was formerly chief financial officer at respiratory-focused biopharma Verona Pharma PLC, and joined Ascension in that capacity, where he served for only months before getting the top-job. Having just completed the annual accounts, Roy understood "where the real value resided" in this highly complex group (previously known as Pro Bono Bio). Over the years, Ascension assembled a diverse range of companies and assets, and a palette of demanding investors, including three Berkshire Hathaway pension funds and Russian state-funded Rusnano, which supports the nanotechnology industry.

As CEO, Roy is focusing on building sales of FlexiSeq, a marketed OTC product for osteo-arthritis joint pain, and on advancing a clinical pipeline of potential treatments for haemophilia A, including PEGylated intravenous and sub-cutaneously-delivered forms of the blood-clotting protein Factor VIII. These assets employ Ascension's proprietary nano-lipid delivery technologies, including the tiny, flexible hydrophilic spheres, known as Sequessomes, that comprise the topical gel FlexiSeq.

Ascension's investors appointed Roy with a clear goal: to build the commercial product business and the pipeline in preparation for a sale. There is unlikely to be a single buyer - FlexiSeq is a consumer-focused product; the haemophilia assets are highly specialist prescription-only treatments. As such, Roy, with a background in economics, accounting and consultancy, is managing lots of different interests and priorities – from the current investors and board, to future investors in both parts of business, and employees. "It's like being a politician on the road, canvassing votes," he said. "Your life is no longer your own."

BIG PHARMA: Mary Kerr, CEO Of KaNDy And NeRRe Therapeutics

Big Pharma is an important and growing source of biotech talent – not only CEOs but development scientists, regulatory and commercial experts and more. Jumping straight from Big Pharma country manager to biotech CEO is not always wise, though, as it may not always provide the relevant experience working as part of a senior management team and dealing with a board and investors.

Mary Kerr, CEO of NeRRe Therapeutics Ltd. and KaNDy Therapeutics, did move directly into the top-job after 20 years at GlaxoSmithKline. But she had, within GSK, moved towards running "standalone businesses on the edge of the company where I had freedom to operate and could nurture and inspire people to be creative," she said. Kerr set up GSK's European Critical Diseases Unit and ran HIV-focused ViiV Healthcare in Europe, before becoming SVP and global franchise leader for immuno-inflammation and infectious diseases. "I knew I wanted to be in charge," she says. (GSK's experiments with biotech-like, therapy-area-focused R&D structures, with ring-fenced budgets, nurtured other biotech CEOs, too.)

So when the opportunity arose to run a biotech co-founded by GSK colleague Mike Trower, Kerr seized it. Trower, previously VP and Head of External Drug Discovery in GSK's Neurosciences Center for Excellence for Drug Discovery, became CSO of KaNDy, built around neurokinin-1 receptor antagonists bought from GSK.

The company's pipeline initially included programs targeted at neuronal sensitivity disorders such as chronic cough, and at women's health conditions. Some investors wanted more focus, so KaNDy was spun off in September 2017 devoted exclusively to women's health. For that business, Kerr targeted longer-term and crossover investors, including US investor Longitude Capital.

As for the cultural and operational differences between a big pharma and a biotech – they are not an issue, for Kerr. "My integration into biotech has been easy," she said. "Biotech culture suits me a lot better than big pharma [culture], but I can only do what I have done because I learnt my trade in pharma."

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Beyond The Watershed: Gene Therapy Investment And Promise

JANET LAMBERT

Janet Lambert, CEO for the Alliance for Regenerative Medicine recently spoke to *In Vivo* about the tremendous levels of investment the cell and gene therapy industries are attracting, as well as reasons why Europe excels at incubating advanced product development.

BY JO SHORTHOUSE

Globally, companies active in gene and cell therapies and other regenerative medicines raised more than $13.3bn in 2018, a 73% increase over 2017.

Janet Lambert, CEO of the Alliance for Regenerative Medicine, highlights commercial challenges still ahead for this sector even as R&D breakthroughs continue to emerge.

She discusses the atmosphere in the US and Europe, where regulators are trialling different approaches and pathways for these novel therapies as companies seek smooth routes to market.

Question: what do the words Nightstar, Spark and Vivet have in common? The answer: all the names of companies working on development strategies for gene therapies that, together, have piqued the interest of big pharma to the tune of almost $6bn within the last 12 weeks.

Biogen Inc. recently announced it would pay $877m for Nightstar Therapeutics PLC, a deal that will give it access to the gene therapy developer's expertise in retinal diseases. Elsewhere Roche marked its territory at the end of February by agreeing to pay almost $5bn for Spark Therapeutics Inc. to get hold of inherited blindness drug Luxturna (marketed in Europe by Novartis AG and in the US by Spark), and a few hemophilia A candidates.

Pfizer Inc., which has a history of bolting on gene therapy assets, has most recently paid $51m for a 15% share in French gene therapy company Vivet Therapeutics, which is developing a new program for Wilson disease, a rare and potentially life-threatening liver disorder that causes copper poisoning. Pfizer could pay up to $635.8m, including the option to acquire Vivet outright, under the companies' agreement, after Phase I/II data for lead asset VTX-801 is available.

These three deals are the latest incarnations in big pharma's quest to establish strongholds in this emerging area by investing heavily in companies and products that have disease-modifying potential. Investors too, are warming up considerably to the potential return on investment cell and gene therapies can potentially provide. 2018 saw a huge uptick in investment in gene therapy companies, but the path to efficient manufacture and commercial success for these products is still far from clear.

New research from the Alliance for Regenerative Medicine (ARM) found that, globally, companies active in gene and cell therapies and other regenerative medicines raised

more than $13.3bn in 2018, a 73% increase over 2017. This financing surpassed figures from 2015, which according to ARM's CEO Janet Lambert, was a "watershed year" in terms of investment in the sector when it attracted over $10bn in financing.

"The past few years have seen steady year-over-year uptick in investor interest in financing cell and gene therapies – this sector continues to demonstrate sound and exciting scientific and clinical progress, several with astounding and meaningful patient response," Lambert told *In Vivo* in an interview.

Several of these therapies have made it to market in the US and Europe, and both public and private payers have shown at least some willingness to engage in innovative financing and reimbursement approaches. These strides give investors the confidence that scientifically, these technologies are promising, and in some cases proven. "Clinically, these products have and will continue to provide significant improvement over current palliative approaches, and in some cases, provide a viable, durable treatment option where perhaps there was none," Lambert said.

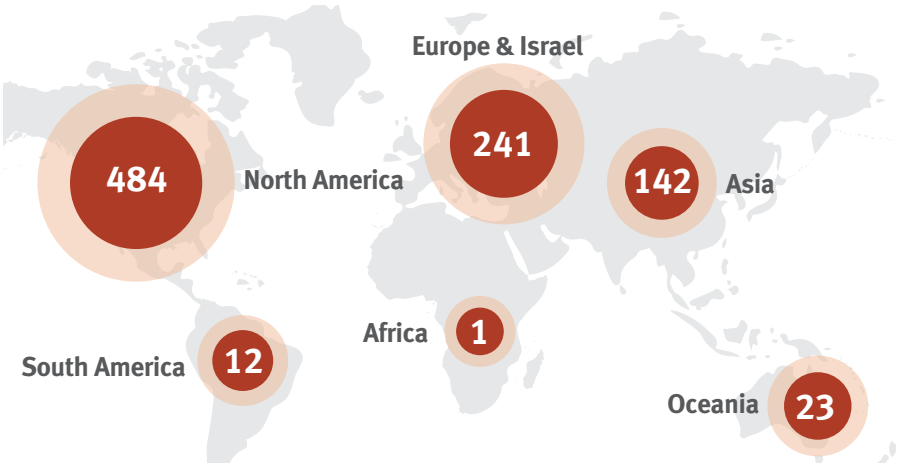
Not only was last year a huge moment in terms of venture capital investment, it was also a standout year for IPOs. To name a few but not all; Allogene floated for $372.6m, Rubius Therapeutics for $277.3m and Orchard Therapeutics for $225.5m. Secondary financing also found a responsive investment community ready and willing to invest; with bluebird bio, AveXis, Iovance Biotherapeutics and Sangamo Therapeutics all raising hundreds of millions to develop their regenerative medicine pipelines.

"We anticipate sustained investor commitment to this space, especially as more product candidates enter the clinic, and as those already there progress towards commercialization," said Lambert. "Commercially, this sector is rapidly and adeptly addressing various manufacturing, industrialization, regulatory and reimbursement hurdles."

While investor enthusiasm is evidently surging, the industry needs to now deliver on its promises and address some of the concerns investors have about return on investment. "We don't have a lot of commercial success stories in this space yet," Lambert told *In Vivo*. "There will be a time when investors will want to see that. They will want to see that these products can come to market, that patients can access them and that it can create a good business opportunity for them as investors. I think right now there's still confidence that all of this will get worked out, but there are still issues that need to be worked out."

Exhibit 1

Global Landscape: More Than 900 Regenerative Medicine Companies Worldwide



SOURCE: ARM's Annual Regenerative Medicine Data Report 2018

> *"Investors will want to see that these products can come to market, that patients can access them and that it can create a good business opportunity."*

ARM is an international community of small and large companies, non-profit research institutions, patient organizations and other sector stakeholders dedicated to realizing the promise of regenerative medicine, globally. It works with its members and policymakers to foster investment, research and development, and successful commercialization of safe, effective, and transformational therapies for patients around the world. ARM's 2018 Annual Regenerative Medicine Data Report details industry-specific statistics and trends from more than 900 leading cell and gene therapy, tissue engineering and other regenerative medicine companies worldwide.

"A lot of what ARM tries to do is to distil a point of view on behalf the advanced therapy medicinal product (ATMP) community globally and share that with policymakers so that they can understand from our broad stakeholder point of view what is it that this community thinks is needed in regulation, reimbursement and manufacturing," said Lambert.

Lambert joined ARM in 2017 as the organization's first CEO. With more than 25 years in public and private sector

management, she most recently served as the acting head of engagement for the All of Us Research Program at the National Institutes of Health and as head of the Outreach Office in the Office of the NIH Director. She has also held legislative and staff leadership positions in the US Senate and House of Representatives.

European Approvals

Three approved ATMPs have created a buzz over the last 18 months: Novartis's Kymriah (tisagenlecleucel), Spark's Luxturna (voretigene neparvovec) and Gilead Sciences' Yescarta (axicabtagene ciloleucel). There are more following their footsteps. The latest nod for a gene therapy came in March, when bluebird bio's gene therapy Zynteglo (formerly LentiGlobin) for beta-thalassemia received a green light from the EU's Committee for Medicinal Products for Human Use (CHMP) meeting – with a final approval expected in the second quarter of the year. bluebird is expected to start marketing the treatment by the end of the 2019.

The marketing authorization application (MAA) review broke records, thanks to the EMA's various programs designed to speed the development and review of potentially ground-breaking products. As Zynteglo seeks to address an unmet medical need, it benefited from PRIME, the EMA's platform for early and enhanced dialogue with developers of promising new medicines. "This interaction led to a more robust application package to demonstrate the medicine's benefits and risks, which allowed accelerated assessment of Zynteglo in 150 days, the fastest advanced-therapy medicinal product review time to date," the agency noted at the time.

Another product expected to come to the European market this year is Kiadis Pharma's delayed leukemia drug ATIR101 (Allodepleted T-cell ImmunotheRapeutics), expected by the middle of 2019. The firm announced in October 2018 that it needed more time to answer questions the EMA had around the company's MAA. However, the potential commercial launch date in a first EU member state remains the second half of 2019. ATIR101 is Kiadis's lead product. It is administered as an adjunctive to hematopoietic stem cell transplantation (HSCT) to provide for a safe donor lymphocyte infusion from a partially matched family member without the risk of causing severe graft-versus-host-disease. The product's T-cells help to fight infections in remaining tumor cells as the immune system regrows.

> *"A big mountain that developers are still trying to climb, even with all the work in oncology, is to try to make progress in solid tumors."*

Expected by the end of 2019 is Novartis/AveXis' therapy Zolgensma for spinal muscular atrophy type 1. And it is anticipated that Orchard Therapeutics will file a MAA in Europe for its gene therapies in adenosine deaminase deficiency and metachromatic leukodystrophy in 2020.

Therapy Areas

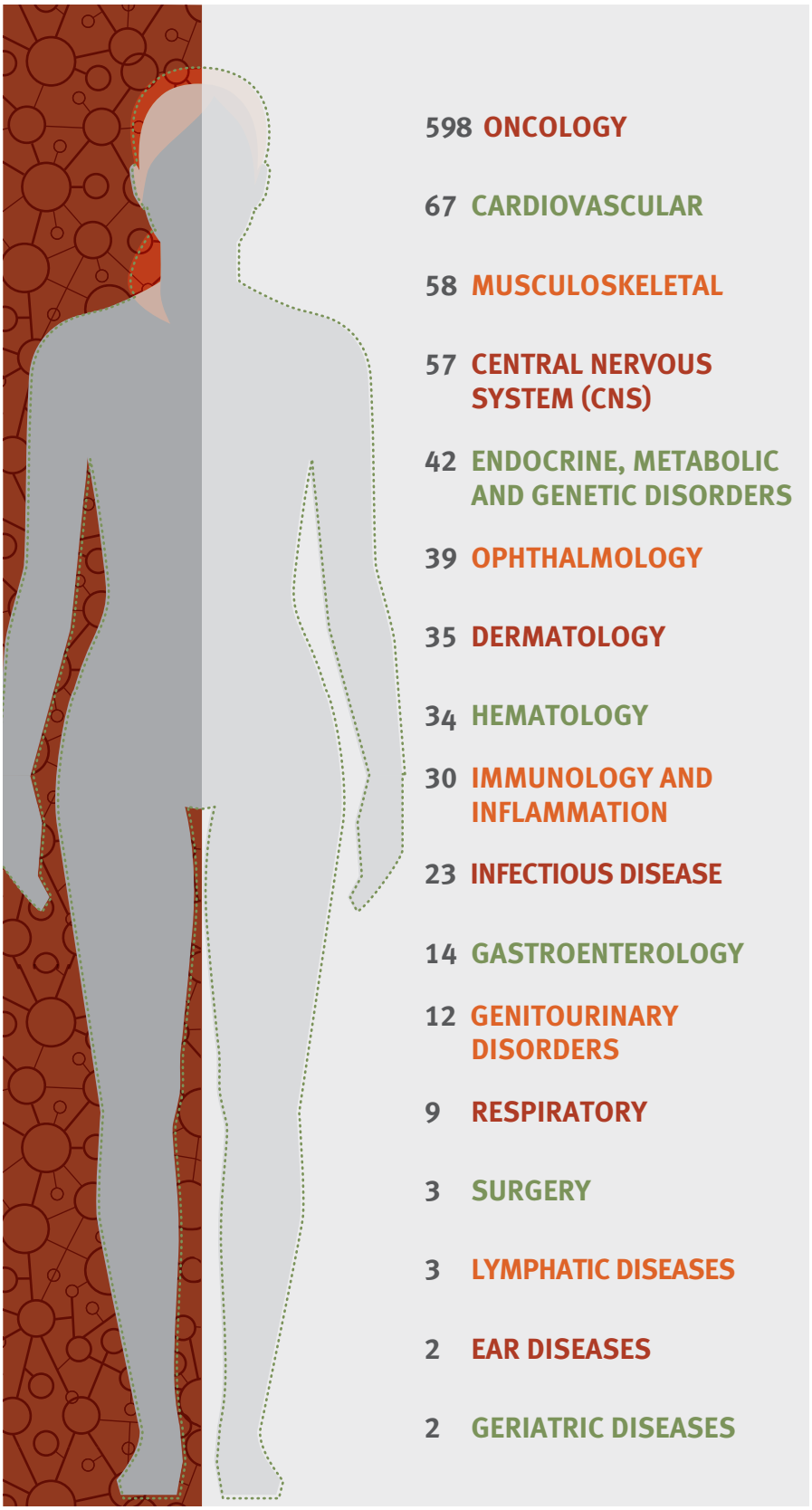
According to ARM, globally there were 1,028 clinical trials underway in 2018 that utilized specific regenerative medicine or advanced therapy technology. Gene therapy trials numbered 362, while cell therapy came to 263, with tissue engineering clinical trials amounting to 41.

"Right now, if you look at the clinical trials that we're tracking, over half of them are in oncology," explained Lambert. "Most of those are in liquid tumors and blood cancers, one of the areas of really early progress in cell and gene therapies. A big mountain that developers are still trying to climb, even with all the work in oncology, is to try to make progress in solid tumors. I think there's a lot of promising work in that area but that will be a very key development in cell and gene therapy."

Lambert remarked that, after oncology, rare diseases that have a genetic basis are an obvious therapeutic area for ATMPs to be impactful. Gene therapies, with their ability to correct a genetic mutation instantly, have applicability across a whole wide range of rare diseases. "It's impossible not to be moved by the plight of patients with rare diseases, and especially because so many of them are children," said Lambert. "It's so compelling, you really, really want to make progress in that space. I think we see in our membership a lot of companies are working in this space and have very strong relationships with the patient advocacy community around them. There's just a lot of scientific promise, as well as human motivation to really solve problems in rare disease," she said.

There is also a lot of work being done for diseases in the central nervous system, in Parkinson's disease for instance, by companies such as Voyager Therapeutics. The pharma industry's major challenge in developing therapies for neurodegenerative diseases that require frequent doses of large amounts of antibodies has been their delivery across the blood-brain barrier (BBB). Cambridge, Massachusetts-based

Exhibit 2
ATMP Clinical Trials By Disease Area: 2018



SOURCE: ARM's Annual Regenerative Medicine Data Report 2018

Voyager has changed this approach by aiming to deliver a one-time intravenous dose of the genes that encode for the production of therapeutic antibodies using its BBB penetrant adeno-associated virus (AAV) capsids. This approach could result in the potential for higher levels of therapeutic antibodies in the brain compared with current systemic administration of antibodies.

Big pharma has been ratifying and investing in this approach, with AbbVie collaborating on both Parkinson's and Alzheimer's disease programs, while Sanofi-Genzyme has taken a keen interest in Voyager's work in Huntington's disease. Meanwhile, Bayer AG has invested in BlueRock Therapeutics, which has a cell therapy program in preclinical development for Parkinson's disease. BlueRock is currently discussing the design of a Phase I trial for this cell therapy candidate.

That said, Lambert noted that the second most common therapy area in the current clinical trial landscape, after oncology, is cardiovascular (*see Exhibit 2*). "It's not something people think about [in relation to gene therapy] but there's a great deal of work going on in cardiovascular disease and some pretty promising clinical outcomes there." Companies such as Cleveland-based Athersys and Casebia – a joint venture created at the end of 2015 by Bayer and CRISPR Therapeutics AG – are active in this therapy area yet taking very different approaches.

Casebia is engineering Cas9 nucleases with specific features to enable both viral and non-viral delivery technologies for its *in vivo* and *ex vivo* delivery of gene-editing therapies in hematology, cardiovascular disease, ophthalmology and autoimmune diseases. While Athersys is working on a Phase III trial to test its off-the-shelf cell therapy MultiStem in ischemic stroke.

MultiStem is manufactured from adult stem cells collected from bone marrow or other tissue donations. The cells can be expanded to produce millions of doses from a single donor, which can be frozen for years before use. Patients enrolled in the Phase III study will receive a single intravenous dose of MultiStem or placebo within 18 to 36 hours of experiencing a stroke on top of the standard of care. The primary endpoint is an assessment of disability according to modified Rankin Scale (mRS) scores at three months and

will compare the distribution of disability for MultiStem-treated patients versus those who received a placebo.

Administration of MultiStem cells is expected to stop the immune system's hyper-reaction to ischemic stroke, by stopping immune cells from rapidly leaving the spleen and heading to the brain, and to concurrently upregulate reparative efforts. Phase II results showing improvements in post-stroke disability at 90 days and beyond supported a Regenerative Medicine Advance Therapy (RMAT) designation from the FDA. Athersys is also testing MultiStem in a Phase II trial in heart attack and a Phase I/II study in acute respiratory distress syndrome.

European Market Access

"Overall globally, but also in Europe, the governments have been really engaged, supportive, and working hard and collaboratively to create a policy environment for this sector," remarked Lambert. "I think that's really a function of a general excitement about the clinical results that we're seeing in the early products in this sector."

The European Commission and the EMA, for example, have developed a specific ATMP plan of action and they worked closely with ARM and other stakeholders to pull together a comprehensive review of what can be done to facilitate the introduction of these products in the European market. In addition to this, in February the EMA issued draft guidance on investigational ATMPs, which makes a clear distinction between exploratory and confirmatory clinical trials, as the traditional approach of distinguishing between various stages of a clinical trial is not as well defined for such products. The guidance is out for consultation until August. *(Also see "EMA Consults On Data Requirements For Cell And Gene Therapy Trials" - Pink Sheet, February 25, 2019.)*

With the EMA leading a Europe-wide co-ordinated effort for the authorization of advanced therapies, it is also starting to weigh in on Health Technology Assessments, Lambert said. "The European Commission is working with stakeholders to see if there are ways that there could be EU wide co-ordination of the scientific part of health technology assessment for ATMPs," she said. "Obviously there would be some unique parts of each country's HTA assessment, but mainly there are some parts of the scientific review that could be shared among the member states, creating efficiencies both for the member states as well as obviously for the sponsoring companies."

> *"We've had a period of incredible scientific innovation. Now we need commercial innovation for this sector."*

Lambert is impressed with the many ways various European governments have been responsive to granting market access to ATMPs. New access schemes must be creative, because these therapies are not the typical medications you can take in a pill form once a day until you are cured. These are expensive one-time product with a long-term benefit, and this throws up unique challenges.

Commercial innovation is required too, she said, which involves government decision making. She cited Italy as an example, where the Italian Medicines Agency will only pay the €594,000 price tag for GlaxoSmithKline's Strimvelis, a gene therapy to treat ADA-SCID, if the therapy works in a patient.

"We've had a period of incredible scientific innovation. Now we need commercial innovation for this sector," Lambert told *In Vivo*. "That is like figuring out how to scale up manufacturing; how to have a distribution network that's both personalized but also efficient." She added that from a reimbursement and market access standing, the industry needed to still figure out how it can work with public and private payers to "effectively integrate these kinds of products into the health care system as we know it, and to do so in a way that is financially sustainable and delivers real access to patients."

In one of the latest developments in gene therapy reimbursement, Novartis and GWQ, a group of German health insurers, announced a pilot scheme in March that will see the Swiss pharma firm repay some of the cost of its CAR-T cell therapy Kymriah if survival outcomes are not met. According to Novartis and GWQ, it is the first outcomes-based deal for an anticancer gene therapy and CAR-T therapy in Germany.

In the US also, the FDA has been as "forward leaning" to the potential of ATMPs as the European governments and policy makers. Lambert said that ARM has been made aware that the FDA has been trying to fill at least 30 new positions in and around cell and gene therapy.

Each geography has its unique set of challenges, the recent US government shut down, for example, makes a career in government service seem a little less attractive, and on the other side of the Atlantic there is of course Brexit, and the upheaval of moving the EMA headquarters from London to Amsterdam which creates personnel roadblocks.

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Rentschler Biopharma: Growing And Innovating As A CDMO Business

FRANK MATHIAS, CEO

Frank Mathias, CEO of Rentschler Biopharma, a contract development and manufacturing organization, talks to *In Vivo* about the company's new corporate strategy and why he allowed 18 months to prepare that plan for delivery.

BY LUCIE ELLIS

CEO Frank Mathias talks broadly about the contract development and manufacturing landscape in Europe and how Rentschler Biopharma is differentiating itself from the competition.

Rentschler Biopharma is a mid-sized player in the CDMO arena but has plans to grow its reach outside of Europe. Keeping his finger on the pulse, Mathias discusses what he thinks lies ahead for the CDMO sector as the biopharma industry continues to evolve its approach to novel treatment of disease.

So what? To stay ahead of the game, Rentschler Biopharma's CEO believes the relationship between biopharma and manufacturer needs to evolve to be more of a strategic partnership. In parallel, CDMOs are likely to serve fewer biopharma customers but under longer term and repeat deals.

Founded in 1927, Rentschler Biopharma is an independent, family owned company headquartered in Laupheim, Germany. Mathias joined the company as CEO in 2016, prior to which he was chief executive of Medigene AG. Since taking the helm of Rentschler Biopharma, Mathias has been focused on preparing the company for the next decade of contract development and manufacturing. One trend he noted as an important change and opportunity to the CDMO sector was the move by pharmaceutical companies toward outsourcing R&D arrangements. "More and more we find that companies are deciding not to take on production themselves, but they give it out, and we can profit from this action. It happens that we have more demand for our services than we have capacities available," Mathias said.

Despite this positive trend, Mathias noted that Rentschler Biopharma also faces greater competition now than in previous times. "The competitive environment around CMOs and CDMOs will certainly become tougher in the upcoming years. A lot of capacities have been built up around the world, within other manufacturing firms and within pharma companies. There's really a lot ongoing, so this is one challenge for us and the sector," he noted.

Alongside this, the needs of Rentschler Biopharma's clients are shifting. "The whole market is changing and there are various new therapies coming in. We have cell therapies, we have gene therapies and we have even more complex molecules." Although challenging, Mathias noted that "at the same time this is an opportunity for us because we have a strong track record with such complex molecules, which is not the case for a lot of our competitors."

Doing Your Research

When Mathias joined Rentschler Biopharma three years ago, he was asked by the supervisory board to develop a comprehensive strategic outline for the company for the coming decade. While this type of activity can be completed in a few weeks and be centred around financial goals, Mathias said the company decided to go another way. "If we want to know what our company might look like in 2025, we need to first understand how the world might be by 2025. This is not so easy to predict," he explained.

Firstly, the company analyzed the 12 so called "mega trends" affecting our society, including the health care sector, such as "silver society." Mathias said, "People are becoming older but want to stay healthier. This is a very positive trend for us." Another trend is interconnectivity, how IT and artificial intelligence technologies are changing the world. "We looked at all these mega trends, for each of them we asked ourselves, "What does this mean for society in general and what does it mean for our company?" He added that Rentschler Biopharma's leadership team took these trends and assessed how the company needed to adapt. "After taking all of these mega changes into consideration we started to have an interesting discussion about what the world might look like in 2025."

To further build the knowledge base for its new 10-years business plan, Mathias and his management team sought insights from other experts. For example, Mathias visited venture capitalists. "We asked private equity firms where they are investing their money today. VCs are very interesting trend setters. They put their money in different companies today because they expect a return on that investment in seven or so years."

Mathias noted that the company also visited head hunters to ask them about the upcoming generation of talent in the life science sector. "We asked them, "What do we need to change about our leadership?" The way young people want to be led "is totally different from my generation for example," Mathias said.

On this fact-finding tour, Rentschler Biopharma also visited hospitals to speak with medical professors and physicians, asking them questions like: "How are you treating cancer today and how will you treat cancer in 10 years' time?" Mathias noted that while many things will change for the treatment of widespread diseases over the next decade, other features will remain unchanged. "We got a lot of insight from these visits to hospitals."

> *"Our slogan is from gene to vial and from concept to market, so we try to offer a service across the entire value chain"*

Finally, Rentschler Biopharma reached out to CEOs of start ups to ask them about new business models. Mathias said the company spoke with biotechs as well as CEOs of emerging business from other sectors. "We took all this information together and we approached our clients around the world, to ask them what they expected from us. We want to be a company that is really client-oriented," he said, adding that those discussions were "extremely fruitful."

Three Key Findings

Mathias said Rentschler Biopharma had learnt three key messages from its meetings with peers and clients.

Firstly, quality will remain the main driver for success 10 years from now as it is in 2019. "When I say quality, I don't only mean the API or the finished product, I also mean the quality of everything we do. The quality of the reporting we do; the quality of the consultant work we do; the quality of the dossier we give to clients for registration. All this will be extremely important for success in the future."

Secondly, Mathias said the company had learnt more about how communication between clients and CDMOs needed to evolve. "It will be more of a strategic partnership in the future. I predict for companies in our area of business, in the future, we will have fewer clients in total but we will serve those clients in a more strategic way." Mathias cited examples of possible deals where Rentschler Biopharma would become the sole manufacturer for a company's entire pipeline. This has several advantages, including only having to negotiate once and allowing a company to more easily secure manufacturing slots.

Thirdly, Rentschler Biopharma found that the one-stop shop approach would remain favorable. "We were one of the first companies offering this. Our slogan is from gene to vial and from concept to market, so we try to offer a service across the entire value chain," Mathias said. Rentschler Biopharma is already thinking about how it can go one step further by providing additional services that go beyond the vial – such as secondary packaging logistics for example.

The Issue Of Talent

When considering the competitive environment, Mathias has one key concern for the future of Rentschler Biopharma that holds true for the entire industry and that is recruiting the right talent. "Certainly, we have to work hard to attract talent in the CDMO sector. This is

even more the case for us because we are located in a region where there is a lot of competition. We have Boehringer Ingelheim GmbH 15km south from us; we have Teva Pharmaceutical north of us. All of this in a very small region," he noted. "We need to be able to get people to come to us, we need to be attractive for people talent-wise."

Mathias added that human capital played an important role in Rentschler Biopharma's business plan out to 2025. "In the past people were extremely happy to come to a company that had a good name. Today you need to approach young people totally differently. It is about what we can offer them as a challenge in their work. How we can develop them. They want to grow with the company," he said, adding that Rentschler Biopharma had been ranked second within Germany as an employer in the health care sector.

CDMO Innovation

Mathias noted that Rentschler Biopharma was keen to keep evolving the company to be an innovative CDMO business, to be able to offer services that its peers cannot. He cited the company's alliance with Leukocare AG as an example of its work to stay novel and ahead of the curve. Leukocare has developed a Stabilizing and Protecting Solutions (SPS) platform, which provides next generation formulation technology able to increase stability of therapeutic proteins in dry and liquid formulations.

He said Rentschler Biopharma was able to avoid "not invented here" syndrome and accept that there was better innovation to solve a key problem for the business outside of its walls. "We had a formulation department already, but it was not at the level of Leukocare. We closed our formulation department in Laupheim when we entered an alliance with Leukocare. They are now our exclusive partner for the development of formulations, which really brings a competitive advantage to our partners."

Rentschler Biopharma also recently appointed a new senior vice president of process science and innovation. Jesús Zurdo joined the company in January 2019. He will provide scientific leadership for development and manufacturing services from cell-line through to final product manufacturing and will also be responsible for managing key strategic collaborations to ensure Rentschler Biopharma remains at the forefront of innovation and technology. Prior to joining Rentschler, Zurdo was senior director of strategic innovation at Lonza, with a particular focus on enabling technologies for bioprocessing and new therapeutic modalities.

> *"We are not looking for merger and acquisition opportunities. We would prefer to go into an alliance by taking shares, for example, and to continue to work together in partnership."*

Rentschler Biopharma has been a bit late to the game when it comes to cell and gene manufacuturing, but the company is assessing several new alliance options, for example, AI technologies that could make production more efficient. "We are not looking for merger and acquisition opportunities. We would prefer to go into an alliance by taking shares, for example, and to continue to work together in partnership. That's the way we approach innovation."

What Next?

Kick starting its corporate strategy for the incoming decade, Rentschler Biopharma also recently acquired a site in the US. "Until the end of last year, we were a German company, even to say a South German company. However, we have a lot of international clients. Our clients asked about an expansion into the US market and we took this seriously," Mathias said.

In January 2019, Rentschler Biopharma completed the acquisition of a manufacturing facility from an affiliate of Shire plc. The 93,000 square foot site is located near Boston in Milford, MA. It represents the first site for the company outside of Europe.

Mathias noted that the business culture in the US was very different for Rentschler Biopharma. "One of the biggest challenges I see when you bring people together is how you integrate them, how you bring them to the culture of the company, but also to the culture of a country." All employees have been retained at the Milford site, as part of the acquisition from Shire. "An interesting part of our job currently is to integrate our new Milford staff members into the German culture, but also the other way around. We want to integrate some of the Milford culture into our German people."

Rentschler Biopharma's CEO said the Milford acquisition was one step for the company on its journey to become a truly global business. Geographical expansion, innovative services, and company growth are Mathias' goals for Rentschler Biopharma as it enters the 2020s.

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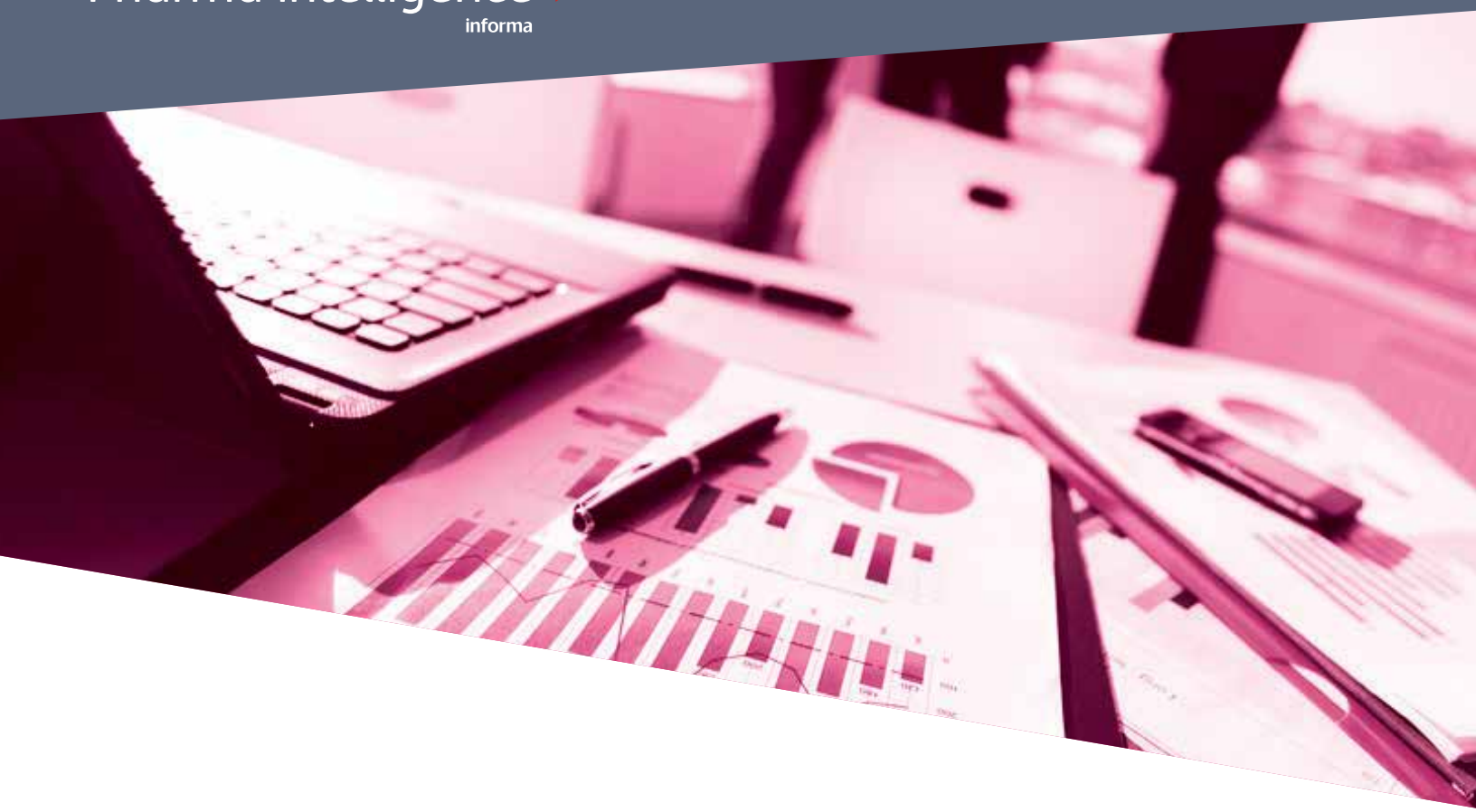

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TISSIUM CEO's Vision Is To Make The Tissue Recon Label Stick

CHRISTOPHE BANCEL, CEO TISSIUM

Christophe Bancel, CEO of French medtech innovator TISSIUM, has made a career in various parts of the health care products industry, identifying business opportunities, founding, directing and leading ventures, and planning for contingencies. The ex-Serono and UCB executive is now testing his adaptability and leadership qualities by bringing a versatile class III synthetic polymer device into key markets.

BY ASHLEY YEO

Spotting the commercial opportunity for meaningful medtech innovation that improves workflow and fits into the value-based health care arena is a particular skill. Driving forward regulatory and reimbursement strategies at the same time requires different types of expertise, but for the CEOs of promising, smaller medtech companies, these roles are often combined.

TISSIUM's Christophe Bancel is one who fits the profile and has his own way of addressing processes. Key for him is that a company's core technology are compatible with a platform-based approach, but this is not always the case.

A sense of realism plus contingency planning are further elements of the leader's skill set.

TISSIUM CEO Christophe Bancel was talking to fellow founder of the company, Jeffery Karp, when the subject turned to a Massachusetts Institute of Technology (MIT) project being developed by Maria Pereira. The technology was a biocompatible liquid polymer, and Bancel was attracted by the claim that it could suture the heart of newborns. Pereira's technology was claimed to support faster healing and obviate the need for traditional suturing.

Seeking to take the idea further, Bancel envisioned a technology ecosystem built around the synthetic polymer, and up to four formulations, initially, to address different clinical needs. Bancel, now 45, already had a track record of innovation development in commercial circles, and had set up the iBionext funding vehicle for start-ups. Evidently, he had the bandwidth for another challenge – one he acknowledged, in an interview with *In Vivo*, is his most exciting to date.

"To start with, we took an indication that was relatively simple – an add-on to vascular sutures – with the idea of spinning the technology out in different directions." With Pereira joining the venture at inception, being central to the company and having since been elevated to chief innovation officer, TISSIUM set about launching a clinical trial in humans. The trial was in 2016; and in 2017, the product was CE marked as an add-on in vascular reconstruction.

Vascular reconstruction was the springboard for the planned wider R&D program extending into new formulations for additional indications that now include peripheral nerve repair, a second-generation specific cardiac application, and, soon, the gastrointestinal (GI) field. The platform element is crucial: Bancel envisaged the company more as a tissue reconstruction specialist than simply a provider of a technology.

Bancel's idea was to do different formulations to match clinical needs using designs

that had a lot of commonality. "We see investment as a fixed cost, and the first step to conquer. We were fortunate to be successful in the first stage of the company's life, and now we're at the second stage – phase 2 – expanding into the portfolio of solutions, and leveraging the activities of the past." Phase 1 of TISSIUM's business plan was validating the technology and getting ready; phase 3 is spinning out new business opportunities, including 3D printing and drug delivery applications.

TISSIUM's business model does not involve selling polymers as a basic component, rather it designs kit solutions. The selling point to clients is that one of its kits will have the right biomechanical properties to allow them to implement solutions that are tailor-made for surgeons.

TISSIUM's first innovative tissue reconstruction product is called SETALIUM Vascular Sealant. Looking to the bigger picture, Bancel decided early on to grow the company by building its own manufacturing capabilities. Its 1,150-m² facility is at a brand-new site in Roncq, near Lille, north-eastern France, and is being set up to produce all versions of TISSIUM's polymer, sterile and ready to use in a pre-filled syringe and packaged in a box with the right accessories for the surgeon.

Contingency Planning

TISSIUM designed the platform in a way that, once successful, it could be scaled up. But contingency plans were also being laid. "You always have in mind that the plan could fail. But with the critical data, we felt relatively strongly that if we were able to translate the technology, it would work." In the early days, the company was producing 5g batches; now it is producing human-grade polymer, class III bioresorbable medical device implants by the kilo.

Bancel admitted that it took TISSIUM "a certain time" to develop the first formulation, but now it has three variations of the polymer, which can be used in different set-ups. It also retains the ability to use the polymer in its liquid form, as a sealant or adhesive. In parallel, it uses the polymer as a resin.

"We pick a specific application and proceed based on user case," explained Bancel. As such, TISSIUM develops everything that supports the user case, knowing that, if successful, it can pivot to other applications, using the same building-block technology. The second application, peripheral nerve repair, is a bid to design nerve conduits that protect the nerve and allow growth inside.

3D Applications

The company can now additionally print 3D medical device implants with extremely high resolution, all bioresorbable in the body. This application is used in the production phase, but it is not yet ready for personalized applications. "The one application where 3D is truly personalized is at the bench, and our technology may lead to that, but not in the short-term," stated Bancel. The approach TISSIUM has selected for its new material is to use 3D printing as a means of manufacturing complex architecture. "Down the road, when we have fully industrialized our capabilities, we will be able to do customization and design specific implants for patients with the same system," he added.

Bancel is clear. "First things first; we must demonstrate that we can make complex medical devices using our own resin with high-quality manufacturing processes using 3D printing. Once the system is validated for a few products, it will be easier to switch to personalized medicine."

User Case Focus

Success in developing medtech innovations requires the core technology to be compatible with a platform-based approach. "That is not always the case. There can be great technologies that are specific and cannot be expanded into a portfolio," Bancel observed. "What we have tried to do is set a long-term vision, typically from a small start, and focus on the user case, pick a specific hands-on project that we can develop and learn from along the way, expand that, and then grow fast. That's the plan."

"We see ourselves as an innovation engine," said Bancel. TISSIUM's strength is its capacity to identify which clinical needs its polymers can provide a solution for. "Now that we have designed an internal process of how to move from R&D to clinical human validation, we can leverage our work across indications. That expedites our work. We learn from experience about how to streamline innovation, and can then go quickly to validation in human clinical trials."

FUNDING TO DATE

TISSIUM raised €8m ($9.04m) in 2013. In 2016, it raised a further €22.5m in a series A led by Sofinnova Partners and Bpifrance. For its series B, the company is planning to raise around $40m.

Learning From Mistakes

Part of the management process involves learning from past mistakes. "We had this vision, based around the planned phases, about how we should design the organization for five or 10 years down the road," explained Bancel. The plan set out how, if TISSIUM is to be successful, the company would make decisions at different time-points to prepare itself for expansion. "That's why we wanted to set up our own manufacturing capabilities. We are a relatively small medtech company and yet, now, we are equipped to serve a breadth of supply needs with a diversity of polymers."

TISSIUM set up its own plant precisely because it did not want to be dependent on certain subcontractors for its very innovative processes. "When you do real core innovation, you don't find people to do what you need them to do – because it's new." He continued, "We had to design new processes for our products – it was complex – but if we were to design effectively, we could use the template for any new product in the future. It was a key asset."

Bancel said TISSIUM had a very strong IP position, including in composition of matter, application and accessories. "And now we also have control of the supply."

The idea is that the more differentiated products that TISSIUM produces, the more it will be able to optimize its costs, controlling both the upstream and the downstream. "And in the middle, we have design processes so that we can accelerate innovation and have exclusivity. "We are a design factory of innovation around our polymers."

A Time To Partner?

But TISSIUM won't do it all by itself. It wants partners in targeted areas,

acknowledged Bancel. "We want to be really good at what we do, and to partner in areas where we are not, so we can learn from others."

TISSIUM's polymers will be available for third parties who want to work with the company, but Bancel feels that these products need to be more than research-grade technology. "If clients want a final commercial solution, we don't want to provide them with a 'half-baked' solution, be they a large medtech or a small start-up."

Partners also need to know that they have protected technology. "The beauty is now we can provide the core platform where the technology is effectively complete, and the partner can go straight to commercialization." TISSIUM wants to partner with companies with products already in place, that have customer bases and know how to approach surgeons in each of the target countries.

Making The Lille Plant Digital

Bancel is determined that TISSIUM remains ahead of the pack and at the forefront of the processes by which businesses evolve. In 2018, it conducted two crucial digitalization projects that ostensibly do not affect current business, but which will make a lot of difference to commercial prospects over time: one focused on the quality system (QS); and the other on financing and supply processes. The plant now shares an enterprise resource planning (ERP) system that had already been implemented company-wide, making it a fully electronic, pay-per-lot facility. This allows the running of projects in parallel without any constraints on quality. The unit also has 300 m^2 of clean rooms (four) and a 140-m^2 analytical laboratory.

The Lille facility is validated, and is running "on hold." Bancel said, "We are waiting to update our dossiers with the new output. The plant has been designed so that we can increase capacity at each of our reactors producing the liquid product, so we can monitor and increase capacity as necessary." The plant employs 12 of TISSIUM's 45 staff, all based in Paris or at the Lille plant.

TISSIUM is working in two geographies, the US and Europe, and is advancing three new products, one is in development, and two in research. All are used in surgical procedures in the OR – hospital-based products – some for open surgery and some for minimally invasive surgery.

TIMINGS FOR REGULATORY WORK

TISSIUM's first product, for use in vascular reconstruction, is CE marked, and the company will start investigational device exemption (IDE) work this year with the FDA. In 2020, TISSIUM will begin discussions with the Chinese authorities. In parallel, it will start clinical trials for its nerve program at the end of next year (2020), and will keep more or less the same program and timings for the other cardiovascular applications. GI is being lined up as a project for 2020–21. The first fundraising proceeds were used partly to secure CE approval of the initial product, while the second injection of funding was used to demonstrate that TISSIUM could "spin" the platform, that is, scale the technology, including manufacturing. "Most companies underestimate the cost and complexity of manufacturing and scale, which enables interaction with third parties. For us, it meant digitizing all our processes, so there were no bottlenecks," said Bancel.

Competitive Landscape

Analyzing where TISSIUM faces rival technologies or procedures means looking at each specific product individually. "From a platform point of view, we are a unique breed, as our polymer family does not have specific competition," noted Bancel. The tissue reconstruction field is not really defined per se, he said, and in TISSIUM's case, it means bringing tissues together to heal in a variety of procedures – GI, open and minimally invasive in certain cases.

There is no competition to TISSIUM in the procedure of bringing the nerves back together. The standard nerve repair process is a complex technique involving suturing. "Our quick and simple technique allows them to be glued together."

Commercial penetration is always a challenge, and clinicians and surgeons need to be convinced of the benefits of the technology. That requires significant effort. "If we are successful, I am sure people will try to imitate us," Bancel said. Accessing in a real-world OR scenario takes a long time, and this is a constraint of the system. "This is something we take into account when we bring our technologies to market."

The current plan is to do soft launches in four selected countries at the end of this year (2019), in the EU and beyond. The reimbursement codes are already available.

TISSIUM Above All

Where does TISSIUM sit in the roster of companies and ventures that Bancel's name and efforts are behind? (*See box, page 29.*) "This is the company that could have the biggest ramification in terms of spread; it's a brand-new material we are working on, and at the raw state. What makes us different is the materials and we have full control of the IP."

The question for the CEO now is how to transfer that raw value into a business that can be monetized and grow into a large sustainable organization. "The challenge is how you scale and manage speed of development. So far we have done a good – not excellent – job." Bancel expressed pride in his team, and said the next two years would be a very exciting time for the company. "That's when we'll unleash the power of the platform."

What If...

The key for Bancel was broaching the "what if" questions, such as: what if we could remove or replace sutures in surgeries? "We believed we could do a much better job, which is why we created the company."

The what-ifs answer the demand pull. "It's not a one-direction process, but that process *should* start from the demand," he stressed. The technology is seen as an enabler. "Our role is as an entrepreneur, making sure we answer the right questions. We always take a lot of time to ensure we can answer the what-if questions now, that is, at the outset."

The other golden rules are to identify both the value of the market and where there is a need, and then make sure that the company can improve the care of the patients. Equally essential, the technology

iBIONEXT – A START-UP STUDIO

Bancel's varied record of health care projects includes being the co-founder of iBionext, a venture that supports health care technology companies from creation to growth, and aims to transform innovation into products for patients. iBionext styles itself as a management company and start-up studio specializing in the creation and development of disruptive health care start-ups. It began in October 2012 with three companies, TISSIUM being one of them, and currently has nine companies, employing 300 people, with some of them showing fast growth. "It was set up by people who were willing to design a place where companies could develop innovative technologies for patients and answer the 'what if' questions," said Bancel.

must improve the efficiency of the health care system by helping the surgeon.

Commercial Plans

As far as the company's commercial plans go, in terms of growth, "We want to have an approach where we can partner with local payers and know the market. We want a selection of specific distributors," said Bancel. The first launch will be defined as a user case. He reiterated that TISSIUM's products have a very strong competitive advantage – as a fully synthetic product and devoid of animal or human proteins, the technology fits well in those geographies that have been looking for products that need to observe local and cultural criteria.

The vascular sealant application is "just the start," and besides cardiac and nerve, GI and ophthalmology applications are among the R&D options for TISSIUM's proprietary technology. The next stages include not just more of its own products, but also designing for third parties, including the larger medtechs. The immediate goal is to use the new chemistry and build the industrial capability to produce the polymer at scale.

One of the advantages is that, for tissue reconstruction, the developer can play with the ratios – with different proportions leading to distinct properties. The polymers are bioresorbable and fully hydrophobic, don't react with blood, and don't dilute, unlike fibrin- and bovine-based sealants. They polymerize on being mixed and on a light stimulus. The texture is user-friendly in surgical procedures. The product moves from its unpolymerized liquid, viscous state into a polymerized, solid yet flexible state.

The Bancel Approach

Driving the whole concept into life, Bancel breathes pragmatism and a flexible approach. "I have very high aspirations for what we're trying to embark on with my team. I am extremely optimistic – but also paranoid! Life will not always treat us easily. We plan for the best and we manage for the worst."

Elsewhere, he said the staff needed to be themselves, a tenet he applies to himself too. "Don't try to be somebody else." He added, "I tend to be hands-off – I trust my team to know what's good for the company. I hire smart people. And I put the right people in the right jobs and that helps us make the right decisions."

But with value-based health care coming onto the agenda – steadily, if not super swiftly – TISSIUM's technology solutions could be seen as fitting well into the concepts that promote affordable, patient-centered solutions. "I hope so – that's what we try to do. What is key is that a product should be assessed on its value – not on its cost. It's about the value that it brings to the system, whichever way that is defined."

The challenge with the value-based approach is that you need to define metrics to be able to define value. "Managing things by cost is extremely easy – it's what we've all been doing until now. But managing things by value needs a definition of value – which can also be subjective. This is maybe why there has been a struggle to get on with VBHC," Bancel opined.

Crucially, he says there is a need to convince people of value, and a need to communicate with data. "At TISSIUM we define products with a very specific value. The one-size-fits-all approach is not the one we want to pursue."

MULTI-TASKING

Christophe Bancel, MSc (Master in Biochemistry and Molecular Biology, University of Tokyo), MEng (Ecole Centrale Paris), MBA (INSEAD, Paris), currently has two jobs, besides the CEO role at TISSIUM; he is both the co-founder and a venture partner of iBionext, set up in October 2012 to support health care technology companies from creation to growth. Before 2012, he was director of BrainEver, a biotechnology company focused on neurodegenerative disease treatments based on a homeoproteins platform; and prior to that he founded Prophesee, a French developer of innovative sensor technology for applications in all fields of artificial vision. He held various roles at UCB, ending a six-year stint there as general manager of the CNS franchise business in France. This was preceded by a 30-month posting managing endocrinology portfolio sales at Serono in France. He started his career in a business development role at the biotech Transgene, after which he co-founded and directed at Faust Pharmaceuticals (now Domain Therapeutics).

The Technology

The original technology for TISSIUM's synthetic polymers came out of research and intellectual property from the laboratories of Professor Robert Langer (MIT), and Professor Jeffrey M. Karp (Brigham and Women's Hospital), who co-founded TISSIUM, formerly Gecko Biomedical, in 2013.

The management team chose to rebrand the company to more accurately reflect its mission. While it was perceived as being focused solely on the development of adhesion technology, recent milestones illustrate the company's dedication to shaping the new era of tissue reconstruction, leading to a brand refresh under the name TISSIUM. TISSIUM competitors include companies like J&J's Ethicon, BD (Bard) and Baxter, among others.

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The Eye Travels Wide: ProQR's Bid For Leadership In The Genetics Of Sight

DANIEL DE BOER

How did a youthful vendor of IT services, faced with a personal exposure to crippling illness, attract some of the best minds in biotech to launch a company with a then-untested RNA technology that today is a contender for leadership in the rarified space of inherited retinal disease? The answer may lie in the ambitiously definitive name that 36-year-old founder Daniel de Boer gave to his enterprise with a mission: ProQR – an active synonym for finding cures.

BY WILLIAM LOONEY

Launched in 2012, ProQR Therapeutics NV has garnered support from a prominent group of advisers, including company co-founder the late Henri Termeer of Genzyme, raising more than $300m from a public listing. The company received a coveted listing on the NASDAQ Biotechnology Index last December.

If biotech has an outsize personality quotient, ProQR CEO Daniel de Boer can certainly qualify, having just been named by the Davos World Economic Forum to its 2019 list of Young Global Leaders, a group dedicated to identifying "new models of leadership in a disrupted world."

So what? ProQR plans to have five clinical programs for genetic eye diseases over the next two years; the highest stakes center on a key read-out of its leading trial candidate sepofarsen, for Leber's Congenital Amaurosis Type 10.

The eye is a pathway to the origins of disease. Its study requires not only expertise in neuroscience but an almost spiritual passion borne of the fact that, without vision, there is none of the light that makes us functional as humans. It stands rightly as among the hardest but most impactful fields in medicine.

Diseases of the eye are one of biopharma's fastest growing therapeutic segments, with more than $22bn in global drug sales annually, according to Datamonitor Healthcare. The eye and its back-end organ, the retina, rank second only to the brain as a focal point for many genetic disorders, which makes them a target for the industry's most advanced gene- and cell-based R&D.

In today's biopharma, the eyes have it – and the search is on for ophthalmology companies with solid science and a strong, clinically differentiated message. One start-up with a direct line of sight to both is Dutch-based ProQR Therapeutics NV, which leads to the inevitable "so what" question: does a persuasive patient advocate backed by some serious cred in academic and industry science have the right stuff to prevail in applying another iteration of RNA repair technology to treat rare inherited eye disorders currently considered "undruggable?"

Now seven years old, and still awaiting its first marketed product, ProQR does meet the criteria for standout status in emerging biotech. It has a visionary founder and CEO in de Boer, driven by his family's own exposure to incurable disease; a supportive cast of advisers from the "Dutch diaspora" of world-class, business-building talent, including the late rare disease legend Henri Termeer; and an inclusive relationship with activist patient stakeholders, who, to an extent that is unusual in Europe, provide financial support and help guide clinical development. Like any start-up, however, ProQR's clinical footprint is still soft and it faces numerous competitors in the RNA platform

space as well as some deep-pocketed rivals like Biogen Inc. and Roche interested in back-of-the-eye genetics.

None of that matters to de Boer, whose entire life was transformed in 2009, when his newborn son was diagnosed with the CFTR/F508del gene mutation that causes cystic fibrosis. "At the time, I was having great success as an IT entrepreneur in the Netherlands, building three companies that focused on solving tough problems on the info services side – it was very hands on, which I discovered was a positive trait I could readily apply to other businesses." As de Boer told *In Vivo*, he faced a more primeval challenge: finding a treatment that might save his son's life. "I decided that going forward, his life had to be my work, so I sold my last IT company and decided to focus my time and resources on helping patients like my son, with rare diseases for which there are few if any treatments." De Boer spent the next two years educating himself on science, drug development and the biotech business. The other aim was to build a network of experts to lend credibility to the ultimate step of establishing a new business – a process that de Boer was already quite familiar with.

Fraternity Of Three

De Boer chose his targets well. On a whim, he flew to Boston and using his credential as a Dutch-based entrepreneur, snagged an impromptu meeting with Genzyme Corp. CEO Henri Termeer, whose openness to meeting new people was well known in both the biotech industry and his native country.He also found common cause with Dinko Valerio, a prominent geneticist at the University of Leiden and a co-founder of two of Europe's biggest biotech success stories: Crucell NV, which was eventually bought by Johnson & Johnson in 2011; and Galapagos NV, a clinical-stage developer of novel inflammation and fibrosis products, now based in Belgium. A third contact was Gerard Platenburg, a fellow Dutch entrepreneur who founded Prosensa NV, an early RNA therapeutics start-up focused on Duchenne muscular dystrophy that was acquired in 2015 by BioMarin Pharmaceutical Inc.

All three ended up being enlisted by de Boer as co-founders when ProQR set up shop in February 2012. Termeer served on the company's five-member supervisory board until his death in May 2017; Valerio is still a member and holds the chair position. Platenburg is currently ProQR's chief innovation officer.

> *"I decided his life had to be my work, so I sold my last IT company and decided to focus my time and resources on helping patients like my son."*

De Boer's brain trust proved instrumental in putting the new company on the radar screen of top investors in Europe. The region's largest life sciences VC, Sofinnova Partners, took an early stake in the business and now owns about 7% of the company's shares. "If word-of-mouth reputation is a quantifiable asset, then ProQR could certainly claim it had the bandwidth to go the distance to a marketed product," observed one investment manager for a US-based VC who serves on the *In Vivo* Editorial Advisory Board. Added de Boer, "At the time I was just a father of a sick child who wanted to make an impact on his life and the welfare of other patients. The Netherlands is a small country and it recognizes entrepreneurs who have contributed to society, so it was less difficult than I had thought to launch a dialogue about my ideas. The local contacts helped prepare me for the pitch to institutional investors and key influencers like Henri Termeer elsewhere in Europe and especially the US."

Early Play For RNA

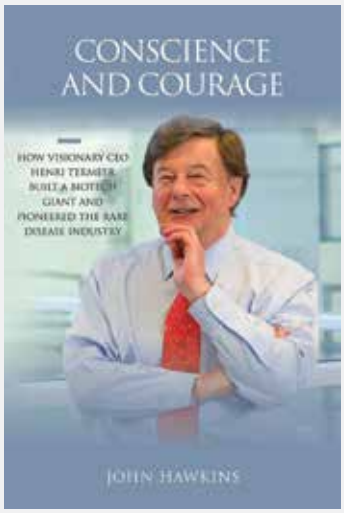
De Boer and his co-founders decided ProQR's business model would center on what, at the time, was a nascent technology for making drugs: ribonucleic acid (RNA), which works to repair genetic deficiencies and thus treat diseases that were undruggable in the traditional small molecule or biologics context. RNA therapies re-engineer cells and proteins rather than editing the genes themselves, with no permanent change to a patient's DNA. That makes them easier to manufacture and safer to administer than a gene-based drug.

Before moving in this direction, ProQR's founders took time to investigate disease platforms without significant levels of engagement by other biotechs. "In RNA, we saw some activity, but it was very narrowly focused. So we started looking down range toward diseases whose causation was driven by a rogue protein, where RNA technology could be applied to restore normal protein expression and reverse the underlying pathology of disease. This became the foundation of our entire research pipeline: using short pieces of single strand RNA (anti-sense oligonucleotides) that can be manufactured synthetically to target genetic defects that contribute to disease. It's pure precision medicine – and the same principle is potentially applicable to multiple conditions," de Boer told *In Vivo*.

It took five years, but in 2017 ProQR established *in vivo* proof-of-concept for its RNA editing platform, which it trademarked under the name Axiomer. It is now being used to guide preclinical testing to correct the RNA in human cells and repair mutations that cannot be treated under current standard of care. The engineered precision in RNA technology makes it a natural for addressing rare diseases, which reinforces the decision of ProQR's founding team to focus on unmet need in this segment, characterized by 7,000 conditions, with treatments available for only a small fraction of them. "We believe the Axiomer platform can repair literally thousands of disease-causing gene mutations in the body. But the fight against rare diseases also benefits from using other RNA-based methods against these inherited mutations. That's why we have a strategic

RARE IS THE DEFINITION OF LEADERSHIP: THE LASTING LEGACY OF HENRI TERMEER

In a recent interview, ProQR's founder Daniel de Boer cited the enormous impact that fellow Dutch businessman Henri Termer played in getting his fledging biotech start-up off the ground – especially given the circumstances. Some 10 years ago, the then twenty-something budding biotech entrepreneur crossed the Atlantic on a chance that Termeer would answer what amounted to an unscheduled desk-knock at the rare disease pioneer's office at Genzyme HQ in Cambridge, MA. He did – and the rest is history.



"I wouldn't say I bluffed my way in, but I was able to score a one-on-one meeting with Henri Termeer the very next morning, which is not the response someone like me, with little name recognition and a mere sketch of a business plan, would normally get from the CEO of a $4bn corporation with 11,000 employees." More important, the initial contact led to a series of door-opening opportunities for de Boer and an eventual agreement by Termeer to sign on as one of three co-founders of ProQR.

The larger truth is de Boer's experience was far from rare, according to John Hawkins, vice-chair of the senior executive and board-level recruitment firm Odgers Berndtson LLC, and a longtime acquaintance of Termeer. Hawkins has spent much of the past two years since Termeer's death in May 2017 working on a biography of the rare disease polymath. Conscience and Courage: How Visionary CEO Henri Termeer Built a Biotech Giant and Pioneered the Rare Disease Industry, is due out on October 1, 2019, and is the product of over 130 interviews with an unusually diverse range of people – in and outside the biotech business, young and old, from patients to health providers to payers; and from the Netherlands to the US and beyond – all of whom knew Termeer and were eager to relay their stories and anecdotes. "Termeer's legacy is immense but not near as well-known as you'd expect," Hawkins said in a recent interview with In Vivo. Not only did he mentor scores of next-generation biotech CEOs, he created the business model in Genzyme that has been widely copied, leading over the past 35 years to the approval of over 500 orphan drugs, covering 700 FDA-granted orphan indications in rare diseases.

"When he joined the tiny start-up Genzyme Corp. in 1983, you could count on two hands the number of marketed orphan drugs available to patients here in the US. That year, on the heels of passage by Congress of the Orphan Drug Act, there was exactly one request from industry for an orphan drug indication. Since then, the number has grown to a total of more than 7,000 to date, and that's largely because of Henri Termeer's leadership in showing how it could be done, to the ultimate benefit of not only his shareholders but the larger patient community as well."

Hawkins devotes a chapter to examples of what he said was Termeer's greatest leadership trait – to turn that imaginary zone of magical thinking into something real, tangible and concrete – and convince others to think and feel the same way. "He was a dreamer, no doubt, but he also had that Dutch quality of modestly staying close to the ground. His decision to contravene the advice of his scientists and VC investors and pursue the development of Ceredase (glucocerebrosidase) for treatment of Gaucher disease was one of the gutsiest decisions every made in the history of the drug industry." As background, Ceredase was the first drug approved as an enzyme replacement therapy, which at the time was a high-risk bet against an inherited disease that is debilitating and, in some cases, fatal – it still has no cure. Enzyme replacement therapy took some time to prove its merit, but today it is an established regimen for a variety of genetic disorders. "Termeer framed his position on Ceredase as a moral imperative – again, something that was novel at the time but today is common in an industry that touts the patient as its purpose." As Hawkins relates in the book, Termeer laid it out starkly for Genzyme shareholders: "the question is whether society wants these very sick patients treated. I think they do."

A promotional campaign for the book begins with a flyer the Biotechnology Innovation Organization (BIO) will include in registrations for the 18,000 attendees at the June 3-6 BIO International Convention in Philadelphia. BIO is also expected to announce an annual leadership award to be offered in Termeer's name. IV124260

commitment to what we call a toolbox approach to RNA, but with the common goal of restoring normal protein expression as the pathway to treatment."

The Eye Looks Back

From his background in the hard-wired business of IT, de Boer believes that, in biotech, therapeutic focus is a prerequisite for commercial success. It explains his biggest strategic bet as CEO to date: to "deprioritize" cystic fibrosis as the company's lead therapeutic target in favor of three inherited degenerative diseases of the eye. "It's true we founded ProQR with my son's condition uppermost in mind," de Boer said. "Cystic fibrosis was our first clinical program, with a molecule eluforsen (QR-010) that we advanced to a small first trial in humans." The results were promising but inconclusive. It became apparent that expanding the trial program to a larger cohort of patients required a major resource commitment. In the meantime, innovative new drugs were being introduced for cystic fibrosis by companies with significant market reach,

with further inroads from RNA modalities designed for the condition by other biotechs. Translate Bio and Ionis Pharmaceuticals Inc., among others, were two companies pursuing similar RNA-based platforms to treat cystic fibrosis. "All told, the number of therapies in play for this disease caused us to take a step back. We remain committed to our original goal of developing multiple transformative RNA medicines for rare genetic diseases, so it is conceivable we could return to this area in the future," de Boer noted.

A further illustration of ProQR's tightened focus is the decision in March to spin out another one of its trial candidates, QR-313, to treat dystrophic epidermolysis bullosa (DEB), a rare skin blistering condition caused by a mutation of the COL7A1 gene. Responsibility for development of QR-313 will shift to a newly formed company, Wings Therapeutics Inc., based in Berkeley, CA. It bears the name of the ongoing WINGS Phase I/II clinical trial for the DEB RNA platform drug initiated by ProQR. Majority control of the company and its asset was transferred to the EB Research Partnership (EBRP), a global non-profit with a mandate to find a cure for epidermolysis bullosa. ProQR will retain a minority stake in Wings Therapeutics and be eligible for royalty rights on any commercialized product.

Market analyst reaction to the repositioning of priorities has been positive, with JP Morgan Securities citing the latter action as a "solid strategic move given the mounting competition and relative market opportunity [versus] the core therapeutic focus in rare ophthalmology."

Why precisely did ProQR's gaze shift to the eye? De Boer said it stemmed from management's commitment to always understand the science first – especially the biologic fundamentals behind each of its therapeutic targets."Our research team spent a lot of time in the lab to optimize the design of the RNA oligonucleotides for stability within the cell and to facilitate delivery of RNA messaging to the right organ. We've also taken advantage of progress in bioinformatics so that we can design medicines on a computer, print them out on a synthesizer and actually test them on human cells." Another factor was the realization that the Axiomer RNA platform proved particularly well-suited to administration of a small molecule drug in a way that can target cells across the entire retina, enhancing the potency of the therapeutic payload in treating diseases of the eye.

That level of detail paid off when ProQR began developing its rare eye disease pipeline. De Boer noted that "one of our biggest achievements was to grow in the lab an accurate model of a human retina, where we could test our computer-designed candidate compounds directly on the retina to determine what aspects of the compound are most efficacious to take into the clinical study. It reduces the steps in the journey from the lab to the clinic, thus helping to de-risk the big investments made to meet trial requirements."

The Retina: Three Ways To Rendezvous

De Boer got excited about ProQR's new mission central: to secure breakthroughs in the field of inherited retinal diseases (IRD). "Its an area of boundless medical need with a disproportionate impact on the most vulnerable populations, especially young children." ProQR's 2018 annual report says there are approximately 300 genetic diseases of the eye, yet only one – Spark Therapeutics Inc.'s Luxturna (voretigene neparvovec-rzyl), for vision loss associated with inherited mutations of the RPE65 gene – currently has an approved treatment.

The new therapeutic line-up was formally unveiled in January 2019, with release of ProQR's "Vision 2023" strategy committing the company to have two commercially marketed IRD drugs and another 10 IRD candidates in various stages of development, by the end of the five-year plan period. In addition, management is promising to position its oligonucleotide RNA platform to underpin preclinical programs in therapeutic areas outside IRD, aided by novel partnering and license arrangements covering opportunities involving non-rare disease targets.

Activity for the next 12 months will center on three IRD clinical programs. The first, and most advanced, is the drug sepofarsen (QR-110) forLeber's Congenital Amaurosis Type 10 (LCA10), currently the number one genetic cause of blindness in children, caused by a mutation in the CEP290 gene. Sepofarsen has received both orphan drug and fast-track designation by the FDA as well as orphan status at the EMA. A small first human Phase I/II trial study completed in September 2018 showed measurable patient improvement in vision after a single injection. This is being followed by a larger pivotal Phase II/III trial, ILUMINATE, involving children over six years of age (and with a side cohort under age six) that should launch within the next three months in the US and Europe, with a final read-out expected by the end of 2020. If successful, ProQR will seek marketing authorization for sepofarsen in both regions and a prospective launch later in 2021.

The second program is a two-candidate thrust against gene mutations known to cause Usher Syndrome Type 2, the leading cause of a condition where blindness combines with hearing loss. ProQR is focusing on reversing vision loss from Usher's by addressing the exon 13 mutation in the USH2A gene. The most advanced of the two candidates, investigational drug, QR-421a, is an oligonucleotide RNA that restores function to the misbehaving usherin protein that causes the syndrome., which affects about 15,000 patients worldwide. Currently, there are no treatments for the vision loss associated with Usher's. QR-421a has received fast-track and orphan drug designation from the FDA; the EMA has granted it orphan status. Within the next few months, ProQR will enroll a Phase I/II proof-of -concept trial, STELLAR, with a read out early in 2020, to be followed by a larger, adaptive multiple-dose trial for projected completion in 2021, with a hoped-for approved RNA drug to rollout in 2022.

The accompanying candidate in the clinical development program, QR-411, addresses another gene mutation associated with Usher's syndrome, c.7595-2144A>G. Plans are not as advanced here, the target population is smaller, at about 1,00 patients, and proof-of-concept trial work is not slated to begin until well into 2020. Like QR-421a, QR-411 is being positioned as a first-in-class medicine.

The third priority program is for yet another IRD, autosomal dominant retinitis pigmentosa (adRP). It is a progressive condition that occurs most frequently in patients between 20 and 60 years old and leads to vision loss and blindness; like the others, there is no approved

treatment. Overall, retinitis pigmentosa has a wide footprint, with more than 1.5 million victims globally, so management is hopeful that a niche position around the genetic foundations of the disease will result in expanded opportunities in this segment over time.

ProQR's adRP investigational drug, QR-1123, is an RNA therapy designed to reverse the P23H mutation in the rhodopsin (RHO) gene that accounts for the vision loss. The next step is to initiate a proof-of-concept trial later this year, for an expected read out in late 2020. Worth noting is the QR-1123 candidate was acquired in an October 2018 licensing deal with rival Ionis Pharmaceuticals, which uses an RNA oligonucleotide platform that is similar in some respects to ProQR's Axiomer. Ionis will receive royalties on revenue accrued if QR-1223 becomes a marketed drug.

Further back in the pipeline cue are investigational candidates for two other IRDs. QR-504 is for treatment of Fuchs endothelial corneal dystrophy, which causes corneal edema and swelling, resulting in clouded vision progressing to blindness. An initial proof-of-concept study is being prepped for launch next year, followed by additional trial work in 2021-22. The other is for Stargardt's disease, the most common inherited form of macular degeneration in children and adolescents leading to vision impairment and loss. QR-1011 uses ProQR's RNA platform to divert mutations in the ABCA4 gene that causes Stargardt's and restore vision.

Can Sepofarsen Seize The Day?

De Boer admitted Vision 2023 was a busy document but expressed confidence that its ambitions lay within reach. "It starts with our lead candidate, sepofarsen for LCA10. "It has evidenced such a significant level of efficacy for patients in trial that we believe it has a good probability of being approved by regulatory authorities in both the US and Europe. These were patients as blind as you can get, who ended up being able to read the number on a bus and move through the routine of daily life in a way they never could before."

De Boer saw this as transformational – and a precedent. "I think we will see progress on the rest of our IRD pipeline, based on that lead program. Across the board, we are committed to keeping pace with the timelines we've laid out for the execution of five IRD clinical studies in the next 18 months. We want to deliver read outs on each of these and end up with two marketed IRD drugs by 2023. That's the target."

De Boer also contested the notion that the company is over-committed to one therapeutic area at the expense of a more diversified portfolio. He asserted that IRD was a rich and varied space – "the eye is very complex and has proven to be the lead point into a range of neurodegenerative conditions that affect two of the largest organs in the body, the brain and the spinal cord. More important, each of our five IRD trial candidates are different products for separate patient populations. There is no overlap."

In fact, ProQR has opted for licensing deals as perhaps a more prudent way of finding additional entry points to diseases that could benefit from its RNA technologies. For example, the company has ongoing agreements with the University of Leiden Medical Center to explore development options in hereditary cerebral hemorrhage with amyloidosis and Huntington's disease, using the RNA oligonucleotide platform. With its strategy set, ProQR's next step is to build a true go-to-market organization with the logistical and talent capabilities to bring multiple products to patients in the clinic. This year began with a spate of new hiring, including the appointment of a chief commercial officer along with senior officers responsible for finance, medical affairs and investor relations and communications – essential roles in the all-important market access space.

Ready For The Market

The company appears adequately financed to make the transition. It went public with a share offering in 2014 and since then has raised $284m on NASDAQ, private placements and loans and grants from a mix of government and private organizations. De Boer also points to a special benefit from its big stake in what others might call an obscure therapeutic segment, even by rare disease standards. "Our therapeutic focus on IRD has brought us strong support from patient advocacy organizations, not only in the enthusiasm and know-how they bring to the science but in the actual funding of some of our most important clinical trials." An example is the February 2018 compact between ProQR and the independent California-based Foundation Fighting Blindness, in which the Foundation will contribute $7.5m to advance QR-421a for Usher Syndrome Type 2 into the clinic.

Of course, there are always wild cards to disrupt the strategy going forward, perhaps the biggest of which is the bet management is placing on a good outcome for the sepofarsen trial for LCA10. It is why many analysts still consider ProQR a high-risk investment, though such an assessment is not unusual in cases where a company has no marketed product. It can also be hard to predict take-up by physician practices in ophthalmology and the impact of competitors in the IRD space, which now include novel entrants like Odylia Therapeutics, a Boston-based IRD company established in March 2018 with help from leading academic institutes and organized as a tax-exempt nonprofit. And there are other uncertainties about potential market size and reach, including how payers might determine the level of access to patients.

The bottom line, the company has over $100m in cash to fund its pending clinical programs well into 2021. And in an external vote of confidence, ProQR obtained in December 2018 a listing on the NASDAQ Biotechnology Index (NASDAQ: NBI). "A NASDAQ listing is important because it gives us more visibility in the US market, where most of the capital and expertise in health care investing is based."

And the view forward? "I am truly convinced that within this complex and growing IRD space we are uniquely positioned to help those patients who have no other options for their condition – that's the reality that drives the passion we have as a company," de Boer said. "And as long as we are convinced that ProQR is the best party do that, we will continue to operate independently – we will not sell the company."

IV124259

Comments:
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Leading In Product Development Means Planning For All Eventualities

MATTEO MANTOVANI

What is the cost of an adverse event, and the resulting safety action for a medical device that is already on the market? It is the kind of question that no company with products on the market wants to have to confront, but it is also one they know they should plan for, says the design consultancy and innovation organization NCS Lab srl.

BY ELENA VARINI* AND ASHLEY YEO

Understanding failure is the most complicated process in a medical device product's life, and a study of it delivers probably the most comprehensive and valuable information a designer needs and should focus on in order to avoid market recalls.

So what? There is a way to use failure investigation at an earlier stage in the design and development process to improve understanding of how devices fail to perform when out in the field, and thereby avoid potentially catastrophic effects.

"Unfortunately, there is still a knowledge gap to fill before we, as an industry, can claim to be compliant with the currently-available performance standards for medical devices: we need to be sure we are able to face compliance issues once the product is on the market." That could be part of the mission statement of NCS Lab srl, a technical assistance and lifecycle research company with over 10 years' experience in the sector.

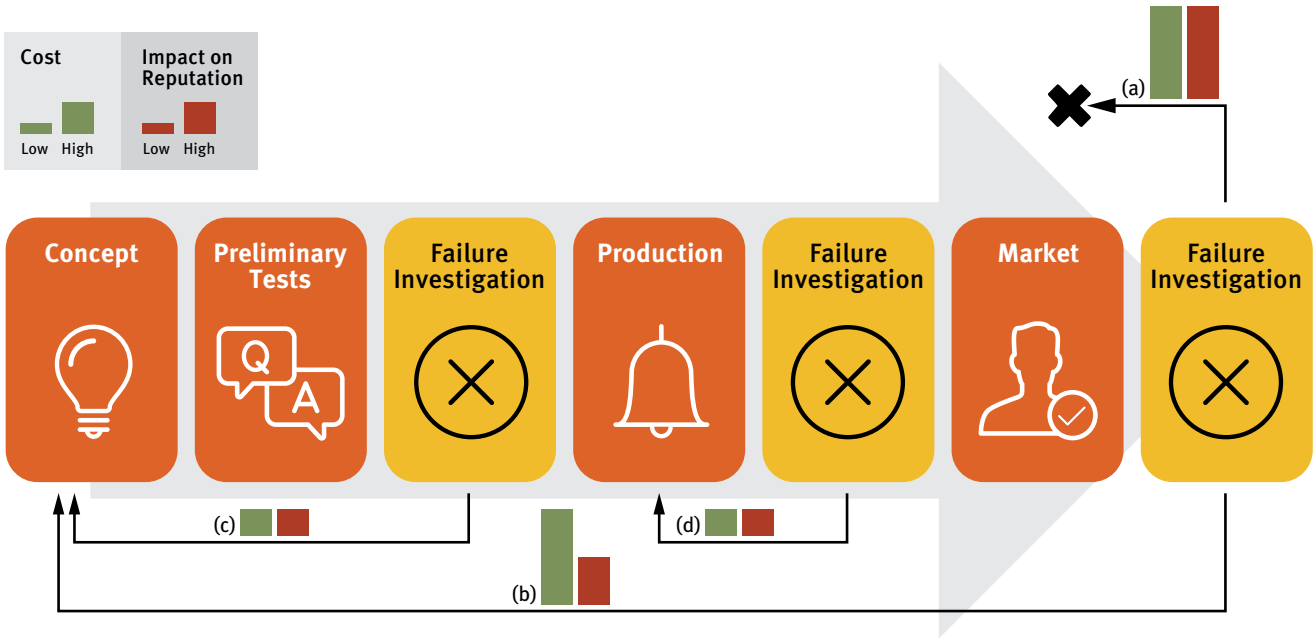
The Italy-based company observes that the evolution of medical device innovation has led to the concept of "mininvasivity," which is a term that embraces miniaturization, incision rescaling and bone stock preservation etc. The push to reduce the impact of surgery is one driver of this development.

But this has brought with it an intrinsic increase in the stress level on devices (due to their reduced dimensions), together with a higher degree of difficulty on the part of the user, where new techniques relating to miniaturization and the constant drive for new technological solutions need to be factored in. Both of these considerations can bring a higher probability of device failure.

The standards apparatus can, in some cases, support and steer technological and oversight developments in an optimal way, but in most cases, the methods of approach are related to the manufacturer's knowledge and experience. But with evolutionary innovation trends leading the way the industry is driving to develop medical devices today, in contrast with the situation in the past, the manufacturer's expertise can be threatened or even be insufficient.

Exhibit 1

Effect On Cost And Reputation Rises Sharply If Failure Analysis Is Done Post-Market Launch



Source: NCS Lab srl

Risk Of Undesired Drift Away From Expected Experiences

Device innovators can therefore witness undesired drift away from expected performance due the fact that current design criteria do not take account of the needs of new devices, but instead are still focused on meeting standards that were appropriate for the "old way." This is relevant for all new device design activity, including the often-inadequately-planned-for activity of failure analysis. That is the view of Matteo Mantovani, CEO and technical director of NCS Lab srl.

He said: "Over many years as a failure analyst, I have amassed a solid experience in understanding how components fail. Despite the thousands of broken parts analyzed, I realized that in the diversified world of medical devices, many competencies are needed to provide a complete understanding of all the facets and concepts involved."

This became clear to Mantovani when he started designing medical devices and realized that he was repeatedly coming across the same problems that needed attention and analysis. He asked himself, how was it possible to keep coming across mistakes that had been seen and analyzed many times before? How could such problems be avoided, and where was the advice?

"The answer to these questions is not obvious and it took me a while to connect the dots and obtain a clear picture from the clues," said Mantovani.

The apparently easy answer is that the mental methodology of design is to blame. But this is wrong. "For some reason in our minds, as in many designers' mindsets, the common default is that failure investigation is the final step in a product's life. Putting attention to it is often perceived as an open criticism of the final product."

Understanding failure is the most complicated process in a product's life, but focusing precisely on this yields what is probably the most comprehensive set of valuable information for designers, giving them all the insight and examples needed in order to avoid recalls from the market.

A failure investigation offers: 1) complete understanding; and 2) the evaluation of a "phenomenon," but it also needs: 3) expert input from a range of sources, spanning from the clinical to materials to engineering departments.

The crucial step is to understand how this information can be truly valued if failure investigation is the last step in the product's life, where the investigation is usually managed by the Quality Assurance or Regulatory Affairs (QA/RA) department. Is there a way to use failure investigation information at an earlier stage to help improve our understanding of how a device performs in the field? Is there an effective way to prevent potentially seriously harmful consequences?

Failure Investigations In Early R&D

The answer to both questions is: yes. Mantovani noted that failure investigations can be used as an R&D tool at the early stages of the development process. This would avoid potentially "catastrophic" events, thereby also lessening the impact of device failures on patients and companies' financial accounts.

Failure mode and effects analysis (FMEA) and, in general terms, risk analysis, are advanced processes that can be very useful in trying to intercept future problems in the product lifecycle. "If we take a close, analytical look at where most of the risk mitigation actions come from, there is a strong correlation between the available standards and problem solutions."

In view of that, several questions arise, such as: Is this a satisfactory solution in a world where the general trend is to drive for extremes both in terms of design and technical functionality?

And isn't this the right time to start

thinking about how to expand development and risk management processes by using the failure investigation as a routinely-conducted activity with the principal aim of collecting additional information, and with the purpose of re-introducing it into the design cycle?

Furthermore, "we need to figure out the range of expertise and the technical background needed to really value the whole range of the information that can be gathered, which is extremely wide."

It is rare that one individual will have a combination of all skills, such as a mechanical engineering background, materials and processes know-how, and clinical expertise. And even if so, it is not common that the individual would have expertise in all these topics to the same level.

The Multidisciplinary Team View

That is why, in a risk analysis process, a multidisciplinary team is needed to be able to assess the project or product from all different points of view in an attempt to capture and deal with non-obvious potential issues that may arise. The same goes for a failure analysis process; in fact, to really analyze the information set and the connection between the elements, a lot of expertise is needed.

So, in view of this, a failure investigation should no longer be the "final act" that must be done merely for legal liabilities or quality compliance. Instead, this most under-valued and under-employed activity should be conducted and planned alongside the product's development, to guard against post in-use failures.

"Based on our experience, and as we now operate in our daily routines at NCS Lab, failure investigation is a design instrument that is used in the development phase as early as possible in the process. That is because we truly believe that understanding technical performance follows a solid understanding of how failures develop," said Mantovani.

A failure investigation in the early stages can provide additional information that is of great help in preventing future problems that can have serious effects. In many situations, the set-up chosen for product performance verification is inappropriate and not completely representative of working under real-world conditions. Despite this, a failure investigation carried out on samples can, most of the time, provide evidence, including non-obvious details, that are extremely valuable for a complete design evaluation.

NCS Lab's laboratory manager, Andrea Vecchi, added, "The approach developed by NCS Lab for failure analysis combines design engineers, materials and processes experts, application engineers and clinicians to exploit fully the information collected. We then use this to interpret the issue and evaluate the connection between design input and product performance."

Under this approach, and in line with the recognized added value of this critical activity, it is possible to redefine failure investigation as a "complete comprehension and evaluation of a phenomenon" – one that needs competencies spanning from clinical to materials to engineering – with the aim of providing sets of information that are useful in confirming or rejecting performance, working environment and or clinical indications. Understanding the root causes provides a valuable set of updated design inputs that must be considered, and which loop back to the design specification.

Failure investigation, as defined above, is a development tool, which seeks to characterize product performance and isolate product failures at an early stage of in the lifecycle – when the failure impacts only on test specimens and not on patients.

Mantovani concluded: "Based on my experience, this is the real embedded value of managing failure investigations in medical device development. The old concept of using this activity only for compliance to quality system requirements is now seen as pointless and an unjustified cost."

IV124262

**Elena Varini is director, business strategy & operations, at NCS Lab srl*

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MAKING A SUCCESS OUT OF FAILURE ANALYSIS

Matteo Mantovani first became involved in private labs dedicated to failure analysis in Italy in 1999, and to date has founded three innovative companies, including NCS Lab srl, in Carpi, Modena, Italy, in 2008. NCS is a certified research lab that engages in medtech lifecycle research, including, design, testing and failure analysis. He is CEO and director of research at the Italian group, which in 2018 set up a US branch, NCS America Inc. in Dover, Delaware.

Mantovani also co-founded injection mouldings company Mimest SpA, to service medtech industry needs (2004), spearheaded a new platform in shape memory materials (also 2004), and founded Newcast Services srl (2005) to prototype innovative materials and technologies in the motorsport industry. He has a Masters Degree in materials engineering (University of Ferrara) and an MBA from CUOA Foundation.

His career has been characterized by leading R&D activities, exploiting a background in materials science, and taking strong interests and roles in biomechanics, fatigue design and failure analysis. He is described as an executive who needs to have an impact on company strategy organization and growth. Born in Sermide, Italy, in 1972.

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On the Move

Recent executive appointments in the life sciences industry

ALEXANDER AZOY

GIANLUCA CORBINELLI

JOANNE JENKINS LAGER

LI MAO

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Aaron Osborne	Adverum Biotechnologies	Chief Medical Officer	Genentech	Principal Medical Director	1-Apr-19
Gianluca Corbinelli	Aerie Pharmaceuticals Inc	Chief Commercial Officer, Europe	Shire	Vice President, Global Strategy Lead	1-Apr-19
Santosh Shanbhag	Akili Interactive Labs	Chief Financial Officer	Vertex Pharmaceuticals	Vice President, Head, International Finance and Accounting	11-Apr-19
Nadia Dac	Alder Biopharmaceuticals Inc	Chief Commercial Officer	AbbVie	Vice President, Global Specialty Commercial Development	8-Apr-19
Zubair Javeed	Ansell Ltd	Chief Financial Officer	Ideal Standard International	Chief Financial Officer	29-Apr-19
Ian Smith	Artios Pharma Ltd	Chief Medical Officer	Eli Lilly & Co	Senior Medical Director	1-Apr-19
William Jones	Biohaven Pharmaceuticals Holding Co Ltd	Chief Commercial Officer, Migraine and Common Diseases	Takeda Pharmaceuticals Inc	Vice President, Sales and Commercial Operations	3-Apr-19
Amy Winslow	BioPorto Diagnostics Inc	President	Magellan Diagnostics	Chief Executive Officer and President	15-Apr-19
Ilan Daskal	Bio-Rad Laboratories Inc	Chief Financial Officer and Executive Vice President	Lumileds	Chief Financial Officer	2-Apr-19
Michael A. Sherman	Chimerix Inc	Chief Executive Officer	Endocyte Inc	Chief Executive Officer	8-Apr-19
Michael T. Andriole	Chimerix Inc	Chief Business Officer	Endocyte Inc	Chief Financial Officer	8-Apr-19

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CATHERINE MATHIS

ELENA RIDLOFF

SIMON STURGE

SANFORD ZWEIFACH

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Richard Malamut	Collegium Pharmaceutical Inc	Chief Medical Officer	Braeburn Pharmaceuticals Inc	Chief Medical Officer, Head, Research and Development and Senior Vice President	2-Apr-19
John Petersen	Crown Laboratories Inc	Chief Commercial Officer	Sandoz	Head, Consumer Dermatology	8-Apr-19
Catherine Mathis	Enterome	Chief Development Officer	ElsaLys Biotech	Chief Operating Officer and Head, Regulatory Affairs	3-Apr-19
Jan Fagerberg	Enterome	Chief Medical Officer	Fagerberg Oncology SA	Senior Advisor	3-Apr-19
Shannon Murphy	GlobalMed Group llc	Chief Technology Officer	Microsoft Corp	Director, Federal Health Solutions	10-Apr-19
Peter Meikle	Grey Innovation	Chief Operating Officer		Consultant	15-Apr-19
Darren Cline	GW Pharmaceuticals plc	Chief Commercial Officer, US	Seattle Genetics	Executive Vice President, Commercial and Member, Executive Committee	22-Apr-19
Michael P. Gray	Imara Inc	Chief Financial Officer and Chief Operating Officer	Arsanis	President, Chief Executive Officer and Chief Financial Officer	10-Apr-19
Joanne Jenkins Lager	iTeos Therapeutics SA	Chief Medical Officer	Sanofi	Vice President, Head, Global Oncology Development	1-Apr-19
Beni B. Wolf	KSQ Therapeutics	Chief Medical Officer	Blueprint Medicines	Senior Vice President, Clinical Development	16-Apr-19

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Douglas Pagan	KSQ Therapeutics	Chief Financial Officer	Paratek Pharmaceuticals	Chief Financial Officer	16-Apr-19
Simon Sturge	Kymab Ltd	Chief Executive Officer	Merck KGaA	Executive Vice President, Global Strategy, Business Development and Global Operations	1-May-19
Matthew McLaughlin	Oxford Immunotec Global plc	Chief Financial Officer	GE Healthcare, US and Canada	Chief Financial Officer	8-Apr-19
Richard Hague	PolarityTE Inc	Chief Operating Officer	Anika Therapeutics	Chief Commercial Officer	8-Apr-19
Gokhan Batur	Polyphor Ltd	Chief Commercial Officer	Merck & Co Ltd	Executive Director, Global Brand Leader, Antibiotics	3-Jun-19
Amol Chaubal	Quanterix Corp	Chief Financial Officer	Smith & Nephew plc	Chief Financial Officer, Global Operations	12-Apr-19
Steve Pakola	REGENXBIO Inc	Chief Medical Officer and Senior Vice President	Aerpio Pharmaceuticals Inc	Chief Medical Officer	17-Apr-19
John Reardon	Ribometrix	Chief Scientific Officer	HemoShear Therapeutics	Head, Research and Development	10-Apr-19
John Witkowski	Royal DSM NV	President, DSM Biomedical	Bemis Manufacturing Co	President, Contract Molding Services	1-Apr-19
Joel Abell	Scientific Digital Imaging plc	Chief Financial Officer	Ametek Inc	Divisional Vice President, Finance, Electronic Instruments Group	2-Jul-19
Giles Campion	Silence Therapeutics	Head, Research and Development and Chief Medical Officer	Albumedix	Chief Medical Officer	1-Jun-19
Wendy Dwyer	Surface Oncology	Chief Business Officer	Portal Instruments	Chief Business Officer	1-Apr-19
Trudy Vanhove	Surrozen Inc	Chief Medical Officer	Jazz Pharmaceuticals	Vice President, Medical Affairs	11-Apr-19
Scott Plevy	Synlogic	Chief Scientific Officer	Janssen Research & Development LLC	Vice President, Gastroenterology	9-Apr-19
Richard Wooster	Translate Bio	Chief Scientific Officer	Tarveda Therapeutics Inc	Chief Scientific Officer and President, Research and Development	8-Apr-19
Lisa Wittmer	VenatoRx Pharmaceuticals Inc	Chief Development Officer	Theorogen LLC	Founder	4-Apr-19
Li Mao	Xcovery Holdings	Chief Executive Officer	Johnson & Johnson China Lung Cancer Center	Vice President and Head	1-Apr-19
Emmanuel Dulac	Zealand Pharma AS	Chief Executive Officer	Alnylam Pharmaceuticals	Chief Commercial Officer	22-Apr-19

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
Elena Ridloff	ACADIA Pharmaceuticals Inc	Chief Financial Officer and Executive Vice President	Interim Chief Financial Officer, Senior Vice President, Investor Relations and Member, Executive Management Committee	1-Apr-19
Andy Crew	Arvinas Inc	Chief Technology Officer	Senior Vice President, Chemistry	2-Apr-19
Ian Taylor	Arvinas Inc	Chief Scientific Officer	Senior Vice President, Biology	2-Apr-19
Filippo Petti	Celyad SA	Chief Executive Officer and Interim Chief Financial Officer	Chief Financial Officer	1-Apr-19
Patrick J. Crutcher	Cerecor Inc	Chief Strategy Officer	Vice President, Business Development	15-Apr-19
Katarina Flodstrom	Episurf Medical AB	Chief Operating Officer	Chief Regulatory Officer, Regulatory Affairs, Quality and IP	1-Jun-19
Andrew G. Long	INSYS Therapeutics Inc	Chief Executive Officer	Chief Financial Officer	15-Apr-19
John Trzupek	KSQ Therapeutics	Chief Business Officer	Head, Corporate Development and Interim Chief Financial Officer	16-Apr-19
Anna Ljung	Moberg Pharma AB	Chief Executive Officer	Chief Financial Officer	16-May-19
Alexander Azoy	Sienna Biopharmaceuticals Inc	Chief Financial Officer	Corporate Controller	1-Apr-19
Mark Foster	Trice Medical	President and Chief Executive Officer	President	30-Jun-19

DIRECTORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Anne Phillips	AMAG Pharmaceuticals Inc	Director	12-Apr-19
Kathrine O'Brien	AMAG Pharmaceuticals Inc	Director	12-Apr-19
Simon Pedder	Cerecor Inc	Executive Chairman	15-Apr-19
Marijn Dekkers	Ginkgo Bioworks	Chairman and Strategic Advisor	16-Apr-19
Christine Mundkur	Lupin Ltd	Independent Director	2-Apr-19
Sanford Zweifach	Palladio Biosciences	Chairman	3-Apr-19
Alessandro Noseda	RegeneRx Biopharmaceuticals Inc	Director	1-Apr-19
Lori Kunkel	Tocagen	Director	15-Apr-19

ADVISORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Deepak Bhatt	Cereno Scientific AB	Scientific Advisory Board Member	2-Apr-19
Faiez Zannad	Cereno Scientific AB	Scientific Advisory Board Member	2-Apr-19
Gunnar Olsson	Cereno Scientific AB	Scientific Advisory Board Member	2-Apr-19
Niek van Dijk	Episurf Medical AB	Clinical Advisory Board Member	1-Apr-19
Allon Friedman	GI Dynamics Inc	Scientific Advisory Board Member	2-Apr-19

Deal-Making

Covering deals made April 2019

Derived from Strategic Transactions, Informa's premium source for tracking life sciences deal activity, the Deal-Making column is a survey of recent health care transactions listed by relevant industry segment – In Vitro Diagnostics, Medical Devices, Pharmaceuticals, and Research, Analytical Equipment and Supplies – and then categorized by type – Acquisition, Alliance, or Financing.

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IN VITRO DIAGNOSTICS

FINANCINGS

Public offering nets **Natera** $94mm

MEDICAL DEVICES

MERGERS & ACQUISITIONS

Smith & Nephew acquires pressure injury prevention and monitoring device firm **Leaf Healthcare**

ALLIANCES

Weihai Jierui to distribute **ACell**'s wound products in China

Cerevast, **Lantheus** sign deal for retinal vein occlusion device

Glaukos gets US distribution rights to **Santen**'s *MicroShunt*

FINANCINGS

Brainsway nets $25.6mm through IPO of ADSs on Nasdaq

Cerus signs debt facility for up to $90mm; $40mm drawn at closing

EndoLogix nets $51mm via FOPO

Public offering brings in $24.9mm for **PolarityTE**

Silk Road Medical nets $128mm in IPO

PHARMACEUTICALS

MERGERS & ACQUISITIONS

Ironwood spins off **Cyclerion**

Novartis acquires NLRP3 inflammasome-focused **IFM Tre** for up to $1.58bn

Histogenics, **Ocugen** reverse merge to create public ophthalmic-focused gene therapy development firm

ALLIANCES

Alnylam, **Regeneron** ally in RNAi drugs for CNS, ocular, and liver diseases through $1.15bn collaboration

Astellas, **Xencor** team up to develop antibodies aimed at cancer

Avidity Biosciences partners *Antibody Oligonucleotide Conjugates* platform with **Eli Lilly**

Basilea, **Forge** pen antibiotics development agreement

Bayer licenses PRL-targeting antibody to start-up **Hope Medicine**

BioAtla and **BeiGene** co-develop CTLA4 inhibitor; BeiGene gets exclusive global rights

BioDelivery Sciences gets rights to **Shionogi**'s OIC drug in US, Puerto Rico

BioSense Global to develop and sell **Rexahn**'s RX3117 in Greater China

BI, **PureTech** collaborate on I/O candidates in $226mm tie-up

Castle Creek licenses US rights to **Fibrocell**'s FCX007 RDEB gene therapy candidate for up to $135mm

Cipla, **Pulmatrix** team up for *Pulmazole*

Clinigen gets Japanese rights to **GC Pharma**'s *Hunterase*

Lilly sells two legacy antibiotics and manufacturing facility to **Eddingpharm** for $375mm

Everest Medicines licenses exclusive sacituzumab rights from **Immunomedics**

Fulcrum gets global rights to **GSK**'s losmapimod for muscular dystrophy

Gilead becomes **insitro**'s first major partner in deal potentially worth over $1bn

Gilead and **Novo Nordisk** sign trial collaboration for NASH combo therapy

PhaseBio grants **ImmunoForge** rights to sarcopenia candidate

Immunomedics to promote **Janssen Biotech**'s erdafitinib in the US

Variant licenses inflammasome inhibitor from **InflamaCORE**

Salix gets rights to **Mitsubishi Tanabe**'s MT1303

Sandoz gains exclusive rights in some European countries to **Shionogi**'s *Rizmoic*

Pierre Fabre gets *Nerlynx* rights from **Puma**

ReNeuron grants **Shanghai Fosun** Chinese rights to cell therapy programs

Cytovant launches, pens first alliance with **Medigene**; deal value could top $1bn

Miracogen uses **Synaffix**'s ADC platforms for cancer drug development

Financings

Actinium nets $15mm via public offering

Applied Therapeutics files for IPO

Arteaus sells *Emgality* royalties to Royalty Pharma in $260mm financing

Public ADS sale nets $109mm for **Autolus**

Public offering nets $23mm for **Aveo**

BioDelivery Sciences nets $48mm through FOPO

Cortexyme files for IPO

DBV Technologies raises $31mm in public ADS offering concurrent with PIPE

Private placement brings $45mm to **DBV Technologies** concurrent with public offering

Eiger BioPharm nets $46.5mm via FOPO

Mustang Bio enters $20mm venture debt financing with Horizon, gets $15mm up front

Public offering nets $70.3mm for **Gritstone Oncology**

Homology Medicines nets $117.5mm via FOPO

Hookipa goes public netting $78.1mm

Milestone Pharma seeks to go public

Moleculin nets $14.1mm through registered direct offering

NGM completes $61mm private placement to **Merck**, concurrent with IPO

NGM Biopharmaceuticals nets $99.2mm via IPO

Outlook Therapeutics nets $26.8mm via FOPO

PhaseBio nets $46.5mm through public stock sale

Pluristem nets $17.9mm via FOPO

Pulmatrix nets $15.3mm via FOPO

Rocket Pharma nets $86mm via FOPO

Sangamo nets $136.7mm via follow-on

Public offerings of common and preferred shares net $66mm for **Syros**

TherapeuticsMD enters $300mm debt facility with TPG; initially draws down $200mm

Trevi Therapeutics files for Nasdaq IPO

Public offering nets $218mm for **Tricida**

Turning Point nets $178mm in initial public offering

Vaxart nets $6.8mm via FOPO

X4 Pharmaceuticals nets $80.2mm through public offering

Zosano nets $16mm via FOPO

IN VITRO DIAGNOSTICS

FINANCINGS

NATERA INC.

Natera Inc. netted $94m through a public offering of 5.26 million common shares at $19. The company develops cell-free DNA tests, and earlier this year penned a deal with **BGI Genomics**, which will sell Natera's *Signatera* minimal residual disease and molecular monitoring cancer test in China once approved in that country. (*Signatera* is currently a research-use only test.) (Apr.)

Investment Banks/Advisors: Canaccord Genuity Inc.; Cowen & Co. LLC; JP Morgan Chase & Co.; Piper Jaffray & Co.; Robert W. Baird & Co. Inc.

MEDICAL DEVICES

MERGERS & ACQUISITIONS

SMITH & NEPHEW PLC
LEAF HEALTHCARE INC.

Smith & Nephew PLC agreed to acquire **Leaf Healthcare Inc.**, a private US maker of a pressure injury prevention and patient mobility monitoring system, for an undisclosed sum. (Apr.)

The transaction--which S&N will finance with existing cash on hand and undrawn debt facilities--is expected to close in Q2 2019. Leaf is best known for its wearable devices that warn of potential pressure injuries. The Leaf patient monitoring system's disposable sensor wirelessly monitors an at-risk patient's position and movement during a hospital stay. The tracking data is then automated and documented to better manage prescribed turn protocols to avoid pressure injuries such as ulcers. Through a February 2017 agreement, S&N already distributes Leaf's patient monitoring system and at that time made an undisclosed equity investment in the company. Prior to the current transaction, S&N owned 11% of Leaf, according to its 2018 annual report. Leaf's patient monitoring system and related accessories will complement S&N's own advanced wound management business segment, which offers products designed for ulcer treatment with brands such as the *Allevyn*/*Allevyn Life* range of absorbent foam dressings, as well as an extensive portfolio aimed at improving protocols for pressure injury prevention. Also in the wound space, just last month S&N bought regenerative medicines firm **Osiris Therapeutics** (wound healing and tissue repair) for $656m.

ALLIANCES

ACELL INC.
SHANDONG WEIGAO GROUP MEDICAL POLYMER CO. LTD.
Weihai Jierui Medical Products Co. Ltd.

Weihai Jierui Medical Products Co. Ltd. (a division of **Shandong Weigao Group Medical Polymer Co. Ltd.**) will exclusively distribute **ACell Inc.**'s wound matrix products in China and Hong Kong. (Apr.)

The partners will work together on regulatory activities, and once approved, Weihai will market the products in the licensed territories for ten years. The two products--*Cytal* and *MicroMatrix*--are made from porcine-derived urinary bladder matrix, and help to remodel functional tissue in wounds including partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical sites, trauma wounds (such as abrasions, lacerations, second-degree burns, skin tears), and draining wounds. In March, ACell granted **MyungMoon Bio** exclusive rights to sell *Cytal* and *MicroMatrix* in South Korea.

CEREVAST MEDICAL INC.
LANTHEUS HOLDINGS INC.
Lantheus Medical Imaging Inc.

Lantheus Holdings Inc. and **Cerevast Medical Inc.** are teaming up in the area of retinal vein occlusion (RVO). (Apr.)

Lantheus licensed Cerevast exclusive rights to commercialize its microbubble and activation device as part of its RVO technology, which is incorporated into an ocular ultrasound device that improves blood flow in occluded retinal veins in the eye. The collaboration seeks to provide intravenous administration of Lantheus' microbubbles via non-invasive ultrasound delivered across the closed eyelid. The therapy can treat the disease itself as opposed to the symptoms. The RVO technology has IDE and should enter a Phase

IIb trial in H2 2019. It could be launched in 2023. Cerevast will handle all regulatory filings and approvals in the US, Europe, and China, and commercialization. Lantheus is eligible for sales royalties.

GLAUKOS CORP.
SANTEN PHARMACEUTICAL CO. LTD.
Santen Inc.

Under a multi-year deal, **Santen Pharmaceutical Co. Ltd.**'s US subsidiary **Santen Inc.** licensed **Glaukos Corp.** exclusive rights to distribute its *MicroShunt* in the US. (Apr.)

MicroShunt is a minimally-invasive ab-externo device in development for primary open-angle glaucoma (POAG), the most common form of glaucoma in adults 40 years and older. The device is in a US pivotal trial for reducing intraocular pressure (IOP) in POAG patients where IOP is uncontrolled with maximum tolerated medical therapy or where the progression of the disease calls for surgery. The PMA submission is expected this year and, should Santen gain approval, Glaukos anticipates a launch of *MicroShunt* in 2020. Under the agreement, Santen would handle marketing and manufacturing activities.

FINANCINGS

BRAINSWAY LTD.

In its second attempt to list on Nasdaq, **Brainsway Ltd.** (deep transcranial magnetic stimulation device (TMS) for psychiatric, neurological, and addiction disorders) netted $25.6m through its initial public offering of 2.5 million American Depositary Shares (ADSs, with each representing two ordinary shares) at $11 (or $5.50/share). Earlier this month the company announced it planned to sell 2.5 million ADSs at $11.94 apiece, or $5.97/share. (Apr.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Ladenburg Thalmann & Co. Inc.; Oppenheimer & Co. Inc.; Raymond James & Associates Inc.

CERUS CORP.

Cerus Corp. (blood transfusion safety systems) closed a debt facility of up to $90m with MidCap Financial. The agreement consists of a $70m term loan (with an initial $40m tranche taken at closing) and a revolving line of credit worth $5m initially, expandable to $20m in total. The remaining $30m of the term loan is available in two equal tranches, with the first contingent upon Cerus receiving either CE Mark approval for the *Intercept* red blood cell system or a PMA supplement approval for *Intercept* cryoprecipitate, and the second tranche available based on achievement of certain revenue targets. Cerus will use the funds to retire an existing term loan of about $29m from Oxford Finance. (Apr.)

ENDOLOGIX INC.

Endologix Inc. (developing minimally invasive devices for aortic disorders) netted $51.1m through the sale of 7.89 million shares of common stock at $6.61. The company also issued pre-paid ten-year warrants to purchase up to 1.47 million common stock exercisable upon issuance. (Apr.)

Investment Banks/Advisors: Jefferies & Co. Inc.

POLARITYTE INC.

PolarityTE Inc. netted $24.9m through a public offering of 2.97 million common shares at $8.51. The company is developing technology to use a patient's own cells and tissues to regenerate functionally-polarized human tissue, and will use the offering proceeds to support R&D, manufacturing, regulatory, and future commercialization of its projects. (Apr.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.

SILK ROAD MEDICAL INC.

Silk Road Medical Inc. (stroke prevention devices used in minimally invasive transcarotid surgeries) netted $128m in its initial public offering of 6.9 million shares (including the overallotment) at $20, the high end of its anticipated range. Three days prior to the final pricing, the company announced it planned to sell 4.7 million shares between $15-17, and then two days later upped the offering to 6 million shares between $19-20, before pricing at the high end of that range. (Apr.)

Investment Banks/Advisors: BMO Financial Group; Bank of America Merrill Lynch; JP Morgan & Co.; Stifel Nicolaus & Co. Inc.

PHARMACEUTICALS

MERGERS & ACQUISITIONS

CYCLERION THERAPEUTICS INC.
IRONWOOD PHARMACEUTICALS INC.

Ironwood Pharmaceuticals Inc. has finalized the tax-free spin-off of Cyclerion Therapeutics Inc. (Apr.)

Cyclerion will operate Ironwood's soluble guanylate cyclase business, trading on the Nasdaq under the ticker CYCN. Ironwood shareholders will receive one Cyclerion common share for every ten Ironwood shares they hold as of March 19, 2019, and will also receive cash in lieu of any fractional shares of Cyclerion stock that the holders would have received after application of the one-for-ten ratio. Cyclerion will focus on advancing five programs--Phase II olinciguat (IW1701) for sickle cell disease, Phase II praliciguat (IW1973) for heart failure with preserved ejection fraction and diabetic nephropathy, Phase I IW6463 for CNS disorders, and two discovery-stage candidates for liver and lung diseases. The deal was originally announced in January. Ironwood will continue to operate in the gastrointestinal space, building upon the commercial success of its IBS drug *Linzess*.

NOVARTIS AG
IFM THERAPEUTICS LLC
IFM Tre

Novartis AG announced a definitive agreement to acquire privately held **IFM Therapeutics LLC**'s anti-inflammatory medicines-focused **IFM Tre** subsidiary for up to $1.58bn. The transaction is expected to close in Q2 2019. (Apr.)

Novartis will pay $310m up front and up to $1.265bn in earn-outs. Concurrent with **Bristol-Myers Squibb**'s 2017 acquisition of its former parent, **IFM Therapeutics**, IFM LLC was spun off as an independent entity to focus on IFM Therapeutics' non-oncology anti-inflammatory pipeline assets. In July 2018, IFM LLC then went on to launch a division, IFM Tre, with a $31m series A round from Atlas Venture, Abingworth, and BMS. IFM Tre specializes in inhibition of the NOD-, LRR-, and pyrin domain-containing 3 (NLRP3) inflammasome, a multi-protein intracellular innate immune signaling receptor. Normally functioning NLRP3 inflammasome activates an immune response that protects against pathogenic threats, but abnormal NLRP3 inflammasome activation plays a role in the development of various inflammatory conditions. The acquisition gives Novartis IFM Tre's pipeline of three small-molecule NLRP3 inhibitors, including lead compound IFM2427, which recently entered the clinic for indications in chronic inflammatory disorders, including gout, atherosclerosis, and nonalcoholic steatohepatitis (NASH). Phase I studies for IFM2427 are expected to be completed in Q4 2019. IFM Tre also has two preclinical programs, one is a gut-targeted molecule with potential in inflammatory bowel disease (IBD), and the other is a CNS-penetrant antagonist. Novartis says the addition of IFM Tre's assets will complement its own anti-inflammatory development pipeline. Competitors in the NLRP3 space include Irish biotech **Inflazome Ltd.**, which is backed by Novartis Venture Fund and plans to advance multiple clinical trials sometime this year; 2017 start-up **Jecure Therapeutics** (liver fibrosis and NASH); and **NodThera** (founded 2016; inflammatory disease, neurodegenerative conditions, and cancer).

OCUGEN INC.
HISTOGENICS CORP.

Public firm **Histogenics Corp.** and closely held **Ocugen Inc.** have signed a definitive agreement to merge. (Apr.)

Following the transaction, Ocugen and Histogenics stockholders will

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respectively have a 90/10% stake in the merged entity, which will trade on the Nasdaq under the Ocugen name. The company will be headquartered in Malvern, PA and led by Ocugen's current management team: CEO Shanker Musunuri, PhD, interim CFO Susan Drexler, and CMO Dan Jorgensen, MD. No Histogenics employees will continue with the combined company. The board will consist of seven Ocugen-appointed directors. In late 2018, Histogenics announced it was suspending the development of its Phase III *NeoCart* cartilage repair therapy, which was designed to rebuild a patient's own knee cartilage using cartilage cells harvested from the femur. At that time, the firm said it was exploring strategic alternatives including potential restructuring, filing for Chapter 11 bankruptcy protection, or ceasing operations altogether. Ocugen brings to the table several ophthalmic therapies. Its lead compounds are Phase III OCU300 (brimonidine) for ocular graft versus host disease (a condition for which there are currently no FDA-approved therapies) and OCU310 for dry eye disease, also in Phase III. Both programs incorporate Ocugen's *OcuNanoE* technology designed to enhance the effectiveness of front-of-the-eye therapeutics. The platform formulates drug candidates into a unique ophthalmic nanoemulsion and the therapies are expected to have increased tear film stability. Ocugen's preclinical modifier gene therapy platform was licensed from the **Schepens Eye Research Institute** of **Massachusetts Eye & Ear Infirmary** in late 2017. OCU400 is in development for treating NR2E3 mutation-associated retinal degenerative diseases and OCU410 is targeting dry age-related macular degeneration (AMD). Rounding out the Ocugen pipeline is preclinical OCU200 for wet AMD and OCU100 for retinitis pigmentosa. OCU400 and OCU300 have orphan drug designations from the FDA, while OCU100 has orphan drug status from both the FDA and EMA. Investment Banks/Advisors: Canaccord Genuity Inc. (Histogenics Corp.); Chardan Capital Markets (Ocugen Inc.)

ALLIANCES

ALNYLAM PHARMACEUTICALS INC.
REGENERON PHARMACEUTICALS INC.

Alnylam Pharmaceuticals Inc. and **Regeneron Pharmaceuticals Inc.** have agreed to collaborate on the discovery and development of RNA interference (RNAi) therapeutics for ocular, CNS, and liver disease indications. This alliance is the continuation of the partners' discovery collaboration with Regeneron's **Regeneron Genetics Center** (RGC) first announced in March 2018 based on RGC research on HSD17B13, a gene expressed in the liver that is associated with reduced risk of chronic liver diseases, including nonalcoholic steatohepatitis (NASH). (Apr.)

With a goal to achieve target gene silencing in the eye, CNS, and select targets in the liver, the current deal also draws from Alnylam's recent preclinical data demonstrating potent and highly durable delivery of RNAi therapeutics as well as Regeneron's *VelociSuite* technologies. Under the new five-year collaboration, Regeneron will lead the development and commercialization for all eye disease programs, paying Alnylam potential milestone and royalties. For the CNS targets, the companies will together advance and alternate management, with the lead party retaining global development and commercial responsibilities, and both parties having the option at candidate selection to equally participate in potential future profits. The partners will also pursue liver disease through RNAi-MAb combinations for complement-mediated diseases, including a trial collaboration evaluating Regeneron's anti-human complement component 5 (anti-C5) antibody pozelimab (REGN3918), in Phase I for ocular inflammatory and retinal degenerative diseases, with Alnylam's microRNA candidate cemdisiran (ALNCC5), which is in Phase II for paroxysmal nocturnal hemoglobinuria and hemolytic uremic syndrome (both complement-mediated diseases). Regeneron will lead combination development, for which Alnylam gets royalties on any potential product sales. Alnylam is responsible for cemdisiran monotherapy development, for which both companies will equally share investment and potential future profits. For all other liver programs, the partners will alternate leadership and equally participate in potential future profits. Alnylam retains global rights to all other ongoing, unpartnered liver disease indication programs in its pipeline. Regeneron will pay Alnylam $800m up front ($400m in cash and $400m in Alnylam equity through the purchase of 4.44 million Alnylam common shares at $90/share (about market average)). Alnylam could get up to an additional $200m in milestones upon the achievement of clinical proof-of-principle in the eye and CNS programs ($100m for each). During the initial five-year discovery period (which includes an option to extend), the companies plan to advance programs directed to 30 targets, for each of which Regeneron will provide Alnylam with $5m in R&D funding ($2.5m at initiation and an additional $2.5m at lead candidate identification); a total of $150m in R&D funding. The deal is expected to add one-two new INDs (in CNS and ocular targets) per year beginning in 2020.

ASTELLAS PHARMA INC.
XENCOR INC.

Xencor Inc. and **Astellas Pharma Inc.** are teaming up in the development of bispecific antibodies for cancer. (Apr.)

Xencor will use its *XmAb* bispecific Fc domains to create multiple bispecific antibody candidates against an Astellas-chosen target and will characterize the molecules. Astellas is responsible for all development, regulatory, and commercial activities, getting exclusive global rights to the candidates. Xencor receives an upfront payment; development, regulatory, and sales milestones; and high-single to low-double digit royalties (*Strategic Transactions* assumes 7-29%). *XmAb*-engineered candidates retain the beneficial properties of traditional full-length antibodies while having improved half-life and stability and better immune inhibitory activity. Just two months ago Xencor teamed up with **Genentech** to co-develop IL-15 bispecific cytokine therapeutics to which Genentech gets exclusive global commercialization rights.

AVIDITY BIOSCIENCES INC.
ELI LILLY & CO.

Avidity Biosciences Inc. and **Eli Lilly & Co.** will work together on new RNA-based medicines in immunology and other indications. (Apr.)

The partners will use Avidity's *Antibody Oligonucleotide Conjugates* platform, which in contrast to antibody-drug conjugates uses a payload that is highly specific to a disease-related RNA instead of a toxic small molecule designed to kill a targeted cell. The technology combines the tissue selectivity of monoclonal antibodies and the precision of oligonucleotide-based therapies to target genetic drivers of diseases. Lilly pays $20m up front and will make a $15m equity investment in Avidity and will also hand over up to $405m per target in development, regulatory, and sales milestones, plus tiered mid-single to low-double digit royalties. (*Strategic Transactions* estimates 4-29%.) The companies did not disclose a potential number of projects that could come from the deal nor did they discuss specific diseases, though Avidity notes that the technology has shown modulation of disease-related RNAs in conditions of the heart, liver, and immune system, as well as cancer. It also has promising data for muscle diseases including myotonic dystrophy Type 1, and Duchenne muscular dystrophy

BASILEA PHARMACEUTICA LTD.
Basilea Pharmaceutica International Ltd.
FORGE THERAPEUTICS INC.

Forge Therapeutics Inc. and **Basilea Pharmaceutica International Ltd.** are teaming up in the discovery, development, and

commercialization of new antibiotic classes. (Apr.)

The collaboration will use Forge's *Blacksmith* metalloenzyme chemistry platform to develop potent and selective inhibitors against two antibiotic targets that have until now been unexploited and difficult-to-drug. Basilea will pay undisclosed money up front to Forge in exchange for access to *Blacksmith*. In addition, Forge could receive up to $167m per target in development and sales milestones, plus tiered sales royalties. The antibiotics to be developed have potential against multi-drug resistant bacteria. Forge chose to partner with Basilea because of the firm's expertise in global anti-infective R&D.

BAYER AG
HOPE MEDICINE INC.

Bayer licensed **Hope Medicine Inc.** exclusive global rights to develop and sell a prolactin (PRL)-targeting antibody for male and female pattern hair loss, endometriosis, and other disorders caused by dysregulated PRL signaling. (Apr.)

In return, Bayer gets an up-front fee, development and commercialization milestones, and tiered royalties. The IP at the center of the agreement is based on research done by Rui-Ping Xiao, MD, PhD, of the Institute of Molecular Medicine at **Peking University**, with which Bayer has had a relationship (Xiao is also the founder, chairperson, and CEO of Hope Medicine). An inhibitor of the PRL receptor-mediated pathway, the antibody has been tested already in preclinical and Phase I studies, and Hope Medicine plans to start Phase II trials in Europe, the US, and China. Several prolactin inhibitors have been in development and launched in the past for various cardiovascular, neurological, and gynecological conditions. Besides Hope Medicine/Bayer's candidate, the only two prolactin inhibitor programs in the pipeline currently are from **Xoma** (in Phase II for hyperprolactinaemia) and **Oncolix** (in Phase I for ovarian, peritoneal, and fallopian tube cancers). Hope Medicine has just been established, and concurrent with the Bayer deal received an undisclosed amount of series A financing from private equity firms Trustbridge Partners and Qi Rui You Kang.

BEIGENE LTD.
BIOATLA LLC

BioAtla LLC and **BeiGene Ltd.** partnered for the development and commercialization of BioAtla's CTLA4 inhibitor BA3071. The antibody is in preclinical cancer studies. (Apr.)

BioAtla gets $20m up front, an undisclosed milestone for early clinical achievements, and up to $249m in development, regulatory, and sales milestones, plus tiered royalties. The companies will co-develop the project through predefined early endpoints, after which time BeiGene will lead development activities and be responsible for global regulatory filings and commercialization. (BeiGene holds a co-exclusive license for manufacturing globally with BioAtla, and exclusive rights to sell the candidate worldwide.) It also takes on all R&D, manufacturing, and commercialization costs in Asia (ex-Japan), Australia, and New Zealand, and will share all costs, profits, and losses with BioAtla in the rest of the world. BeiGene notes that it is attracted to BA3071 both as a monotherapy and a potential combination therapy with its own humanized IgG4 anti-PD-1 mAb tislelizumab. The deal comes just a month after BeiGene entered a $475m deal through which it gains rights to bio-conjugates discovered by **Ambrx**. BeiGene and BioAtla are not strangers; in February, Yong Ben, MD, left his post as CMO of BioAtla to become BeiGene's CMO.

BIODELIVERY SCIENCES INTERNATIONAL INC.
SHIONOGI & CO. LTD.
Shionogi Inc.

Shionogi Inc. licensed **BioDelivery Sciences International Inc.** exclusive rights to commercialize its opioid-induced constipation (OIC) drug *Symproic* (naldemedine) 0.2mg tablets in the US and Puerto Rico. (Apr.)

Shionogi will receive $20m up front and another $10m in the next six months. BioDelivery will also pay tiered sales royalties. *Symproic* is a peripherally acting mu-opioid receptor antagonist indicated for treating OIC in adults with chronic non-cancer pain, including those with chronic pain related to prior cancer or its treatment who do not require frequent opioid dosage escalation. The drug was launched in the US in 2017 and is also in several Phase III trials globally. It is sold as *Rizmoic* in the EU where it was just approved last month. On the same day of the Shionogi-BioDelivery tie-up, Sandoz received rights to the therapy in Germany, the UK, and the Netherlands. Also concurrent with the deal, BioDelivery netted $48m in a follow-on offering. In late 2016, Shionogi entered a US co-promotion agreement for *Symproic* with **Purdue Pharma**. In June 2018, the parties terminated the agreement and as a result, Shionogi regained full US rights and said it planned to seek a new partner in that territory.

BIOSENSE GLOBAL LLC
REXAHN PHARMACEUTICALS INC.

Rexahn Pharmaceuticals Inc. granted **BioSense Global LLC** exclusive rights to develop and sell its cancer candidate RX3117 in China, Singapore, Hong Kong, Macau, and Taiwan. (Apr.)

Rexahn has the candidate in Phase II for pancreatic and bladder cancers; BioSense will develop it in the pancreatic cancer indication plus up to three additional cancers not previously studied by Rexahn. BioSense pays money up front, up to $226m in development, regulatory, and commercialization milestones, plus tiered royalties ranging from the low-double digits to mid-teens. (*Strategic Transactions* estimates 10-16%.) Rexahn had previously optioned RX3117 rights to **Teva** under a 2009 collaboration, but Teva decided that the compound's potential indications were not a good match with the company's business strategy and the deal ended.

BOEHRINGER INGELHEIM GMBH
PURETECH HEALTH PLC

Boehringer Ingelheim GmbH and **PureTech Health PLC** have agreed to collaborate on the advancement of immuno-oncology (I/O) drug candidates using the latter's lymphatic targeting technology. (Apr.)

The lymphatic targeting platform was developed in the lab of Chris Porter, PhD, of **Monash University**, where it was exclusively licensed to PureTech in 2017. The technology allows for precise immunomodulation by using the body's natural lipid transport mechanisms, bypassing first pass metabolism in the liver, to enable the transport of oral drug candidates directly to the gut lymphatic system. With an initial focus on applying PureTech's technology to a BI-designated compound for gastrointestinal cancers, the parties have agreed to develop new I/O candidates for an undisclosed number of targets. Once candidates enter the development stage, BI will assume full responsibility and provide up to $26m in up-front payments, research support, and preclinical milestones; more than $200m in development and sales milestones; plus royalties on product sales.

CASTLE CREEK PHARMACEUTICALS LLC
FIBROCELL SCIENCE INC.

Castle Creek Pharmaceuticals LLC (CCP) licensed exclusive US development and commercialization rights to **Fibrocell Science Inc.**'s lead candidate FCX007, a cell-based potential gene therapy in Phase II for recessive dystrophic epidermolysis bullosa (RDEB). (Apr.)

Fibrocell originally licensed US rights to FCX007--a genetically modified autologous dermal fibroblast that encodes the gene for type VII collagen (COL7)--from **Intrexon** under a 2012 deal. Caused by a genetic mutation resulting in the production of non-functional COL7, RDEB is a rare dermatologic condition that affects the skin's structural integrity making it prone to severe blistering. Under the current agreement, CCP will cover all development expenses up to $20m prior to the initial biologics license application (BLA) filing; should the $20m threshold be exceeded, the remaining costs will be split 70% CCP/30% Fibrocell. Up through

initial BLA approval, Fibrocell will be responsible for development (including pre-launch manufacturing) with CCP taking over all post-approval development and commercialization activities. Under a concurrent manufacturing and supply agreement, Fibrocell will supply CCP commercial quantities of FCX007. Castle Creek will provide $7.5m up front; $2.5m for the first patient enrolled in a Phase III trial (expected to initiate in Q2 2019); $30m upon BLA approval and commercial readiness; up to $75m in sales milestones ($25m when FCX007 net sales achieve $250m and another $50m upon reaching a $750m sales goal); plus, a 30% royalty on the gross profits. Outside development and manufacturing and supply payments, Fibrocell will pay Intrexon 50% of all up-front, milestone, and profit-share payments received from CCP. The deal adds another candidate to CCP's existing skin disease pipeline, which includes Phase II CCP020 (diacerein 1% ointment) for epidermolysis bullosa simplex as well as three preclinical compounds for rare genetic dermatologic conditions and vitiligo. Fibrocell retains sole ownership of the rare pediatric disease priority review voucher, should one be granted upon market approval of FCX007. It can use the PRV can for priority review for a subsequent NDA or BLA or sell it to another company. Fibrocell expects the up-front payment, along with reduced R&D costs, and existing cash on hand, will fund its operations into Q3 2020 and plans to allocate the funds to progress development of its autologous fibroblast FCX013, a potential cell therapy in Phase I/II for scleroderma. Investment Banks/Advisors: Canaccord Genuity Inc. (Fibrocell Science Inc.)

CIPLA LTD.
PULMATRIX INC.

Pulmatrix Inc. and **Cipla Ltd.** entered into an agreement for the worldwide development and commercialization of Pulmatrix's *Pulmazole* (PUR1900) for allergic bronchopulmonary aspergillosis (ABPA) in asthma patients. (Apr.)

Cipla will pay Pulmatrix $22m up front and gets *Pulmazole* rights in all pulmonary indications. The firms will equally share development and commercialization costs as well as global free cash flow from future *Pulmazole* sales. Pulmatrix is responsible for clinical development of the product, while Cipla gets exclusive commercial rights. To oversee the collaboration the parties will create a joint steering committee comprised of four members from each company. *Pulmazole* is an *iSPERSE* (*inhaled Small Particles Easily ReSpirable and Emitted*) dry powder inhalation formulation incorporating the antifungal itraconazole, which is administered at high therapeutic doses to the lung. The therapy is currently in Phase II. The deal represents Cipla's entry into specialty respiratory segment. There is currently no labelled drug for treating ABPA, a condition affecting more than 2 million patients worldwide. Under the agreement, Cipla also receive a non-exclusive, royalty-free, and sub-licensable license to the *iSPERSE* technology.

CLINIGEN GROUP PLC
Clinigen KK
GC PHARMA

GC Pharma licensed **Clinigen KK** exclusive rights to commercialize its *Hunterase* (GC1111; idursulfase-beta) for intracerebroventricular (ICV) administration in Japan. (Apr.)

Hunterase is an enzyme replacement therapy for Hunter syndrome, also known as mucopolysaccharidosis II (MPS II). The compound is sold in an intravenous injection formulation which does not penetrate the blood brain barrier in adequate amounts. The ICV version delivers the drug directly to cerebral ventricles and reaches the cells of the brain and central nervous system. In a Phase I/II trial, the therapy demonstrated a significant decrease in Heparan sulfate, which causes mental retardation. Earlier this year GC Pharma licensed **CANbridge Life Sciences** exclusive rights to commercialize *Hunterase* IV in China.

EDDINGPHARM INTERNATIONAL HOLDINGS LTD.
ELI LILLY & CO.

Eli Lilly & Co. sold two of its legacy antibiotics--*Ceclor* (cefaclor) and *Vancocin* (vancomycin)--plus a *Ceclor* manufacturing facility in Suzhou, China to **Eddingpharm International Holdings Ltd.** (Apr.)

The purchase price totals $375m, $75m of which was paid up front and the remainder due when the transaction closes later this year or early in 2020. All employees at the manufacturing facility will be able to remain with the site and continue working under Eddingpharm. Lilly doesn't provide annual sales figures for *Ceclor* or *Vancocin*, but the therapies have been on the market for over 20 years. The Big Pharma is off-loading them so that it can better focus on newer drugs in China. Eddingpharm adds to its antibiotics portfolio through the deal, and will sell the products alongside others including *Fortum* (ceftazidime) and *Zinacef* (cefuroxime).

EVEREST MEDICINES LTD.
IMMUNOMEDICS INC.

Immunomedics Inc. granted **Everest Medicines Ltd.** exclusive rights to develop, register, and sell sacituzumab govitecan in China, Taiwan, Hong Kong, Macao, Indonesia, Philippines, Vietnam, Thailand, South Korea, Malaysia, Singapore, and Mongolia. (Apr.)

The licensed candidate is an antibody-drug conjugate comprised of the humanized mAb hRS7 and SN-38, the active metabolite of irinotecan, and is pending US approval for advanced metastatic triple-negative breast cancer. It is also in development for other solid tumors including colorectal, stomach, non-small cell lung, liver, pancreatic, prostate, head and neck, and renal cancers. Everest paid $65m up front and will make a $60m payment upon FDA approval of the candidate. It is also responsible for up to $180m in development milestones, $530m in sales milestones, and royalties ranging from 14-20%. The partners will establish a joint steering committee to oversee the relationship, while Everest is responsible for all costs related to development and commercialization of sacituzumab in its territories. The deal is reportedly the largest single-asset licensing to take place in the Greater China region. Everest adds the ADC to a pipeline of in-licensed candidates for cardiovascular, autoimmune, and infectious diseases.

FULCRUM THERAPEUTICS INC.
GLAXOSMITHKLINE PLC

GlaxoSmithKline PLC licensed **Fulcrum Therapeutics Inc.** exclusive worldwide rights to develop and commercialize losmapimod for facioscapulohumeral muscular dystrophy (FSHD). (Apr.)

In addition to losmapimod, Fulcrum gets the existing drug substance and product materials for use in clinical trials, a right of reference to INDs filed with the FDA relating to losmapimod, and an exclusive license to all related patents and data. For the rights, Fulcrum will issue GSK preferred shares worth a high-single-digit stake in the company (*Strategic Transactions* assumes 7-9%). GSK is also eligible for milestones and sales royalties. Losmapimod (GW856553) is a p38 mitogen activated protein (MAP) kinase inhibitor which Fulcrum expects to move into a Phase IIb trial in FSHD patients in the US and Europe in mid-2019. FSHD is a rare and genetic muscle wasting disorder with no currently approved treatment options. GSK has studied losmapimod in 24 clinical trials across various indications such as cardiovascular diseases, depression, and arthritis. Fulcrum believes the candidate can potentially address the underlying cause of FSHD by decreasing the expression of the DUX4 gene.

GILEAD SCIENCES INC.
INSITRO

Machine learning and big data start-up **insitro** signed its first major deal, penning an agreement with **Gilead Sciences Inc.** for the discovery and development of new treatments for nonalcoholic steatohepatitis (NASH). (Apr.)

Insitro emerged from stealth mode last year and is using its ISH (insitro Human) platform--which applies machine learning, human genetics, and

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functional genomics--to drive drug discovery by generating and optimizing in vitro disease models. The platform can provide key information regarding disease progression and can also suggest candidate targets and predict patient response. Under terms of the three-year deal, Gilead pays $15m up front and near-term payments of up to $35m for undisclosed operational milestones. It can move forward up to five targets discovered with the insitro technology, and is responsible for $200m in development, regulatory, and sales milestones per target, plus up to low-double digit tiered royalties. Insitro retains an option to co-develop and co-promote targets in the US, obtain profit-share in China, and get milestones and royalties for sales in other ex-US territories. Insitro's CEO Daphne Koller announced the creation of the company in May 2018, noting that the firm's investor base included Arch Venture Partners, Foresite Capital, a16z, GV, and Third Rock Ventures. Concurrent with the Gilead deal, insitro revealed additional backers (Alexandria Venture Investments, Bezos Expeditions, Mubadala Investment Company, Two Sigma Ventures, and Verily) and that the series A round that closed in May amounted to over $100m.

GILEAD SCIENCES INC.
NOVO NORDISK AS

Gilead Sciences Inc. and **Novo Nordisk AS** signed a trial agreement to study a triple combination therapy for nonalcoholic steatohepatitis (NASH). (Apr.)

Novo contributes its *Ozempic* (semaglutide) to the deal; the GLP1 agonist is marketed for diabetes and is also in development for NASH and obesity. Gilead brings the farnesoid X receptor agonist cilofexor (Phase III for primary sclerosing cholangitis and Phase II for NASH and primary biliary cirrhosis) and firsocostat, an acetyl coenzyme A carboxylase inhibitor that it is studying in Phase II for NASH. The partners plan to conduct proof-of-concept studies on the cilofexor/firsocostat/semaglutide combination for NASH and could also work on additional preclinical NASH research. The deal will help the companies investigate the utility of drug combinations that target the metabolic, inflammatory, and fibrotic effects of NASH.

IMMUNOFORGE CO. LTD.
PHASEBIO PHARMACEUTICALS INC.

PhaseBio Pharmaceuticals Inc. granted **ImmunoForge Co. Ltd.** exclusive global rights to develop and sell the GLP-1 agonist PB1023 for all indications, including those related to sarcopenia and specifically excluding diabetes, obesity, and nonalcoholic steatohepatitis. (Apr.)

PhaseBio gets money up front, plus milestones and mid-single digit royalties on sales by ImmunoForge and any future sublicensees. (**Duke University** is entitled to a portion of the royalties under terms of a previous agreement.) PhaseBio had been developing PB1023 for hyperglycemia associated with Type II diabetes, but ceased work on the candidate, though it still retains rights in that area. ImmunoForge will now develop it for conditions related to the skeletal muscle tissue degeneration disease sarcopenia, adding to its pipeline which includes candidates for senile sarcopenia, amyotrophic lateral sclerosis, cancer cachexia, Parkinson's disease, and Duchenne muscular dystrophy.

IMMUNOMEDICS INC.
JOHNSON & JOHNSON
Janssen Biotech Inc.

Immunomedics Inc. will promote **Janssen Biotech Inc.**'s once daily fibroblast growth factor receptor (FGFR) kinase inhibitor erdafitinib for metastatic urothelial cancer in the US. (Apr.)

Under the agreement, Immunomedics' sales team will provide detailing services to Janssen from the launch of erdafitinib through the end of Q1 2020. (Immunomedics is only required to support erdafitinib in first position detail until the FDA approval of its own cancer drug sacituzumab govitecan, which is currently pending US approval in advanced metastatic triple-negative breast cancer but is also in various stages of development for multiple other cancers.) Janssen will pay low-double-digit sales royalties (*Strategic Transactions* estimates 10-29%) and sales milestones in 2019 and 2020, subject to sales thresholds in each year. The FDA is currently reviewing the NDA for erdafitinib in treating patients with locally advanced or metastatic urothelial cancer and certain FGFR genetic alterations whose tumors have progressed after prior chemotherapy. Erdafitinib received breakthrough therapy designation in the US in March 2018.

INFLAMACORE LLC
VARIANT PHARMACEUTICALS INC.

InflamaCORE LLC granted **Variant Pharmaceuticals Inc.** exclusive global rights to develop and sell its inflammasome inhibitor IC100 and related projects for inflammatory disease. The license also includes a potential companion diagnostic. (Apr.)

IC100 is a monoclonal antibody that targets the ASC component of infammasomes that activate the body's innate immune response. By inhibiting intracellular ASC, IC100 blocks initiation of the inflammatory cascade. The candidate has shown positive preclinical data in a variety of indications, including spinal cord injury, traumatic brain injury, stroke, acute lung injury, rheumatoid arthritis, and multiple sclerosis. Variant will study IC100 alongside its pipeline of candidates for renal and inflammatory diseases. The company's lead renal candidate VAR200 is entering Phase II for focal segmental glomerulosclerosis (FSGS), and it is also working on a potential treatment for Alport syndrome, as well as ASC inhibitors for lupus, diabetic kidney disease, and NASH.

MITSUBISHI CHEMICAL HOLDINGS CORP.
Mitsubishi Tanabe Pharma Corp.
BAUSCH HEALTH COMPANIES INC.
Salix Pharmaceuticals Ltd.

Mitsubishi Tanabe Pharma Corp. licensed **Bausch Health**'s **Salix Pharmaceuticals Inc.** exclusive rights to develop and commercialize MT1303 (amiselimod) worldwide, excluding Japan and certain other countries in Asia in all fields, with the exception of neurology, rheumatology, and certain rare dermatology diseases where Mitsubishi Tanabe retains the rights. (Apr.)

Mitsubishi Tanabe receives an undisclosed up-front payment, development and regulatory milestones, and sales royalties. MT1303 is an oral sphingosine 1-phosphate receptor antagonist for various indications including inflammatory bowel disease (Phase II) and ulcerative colitis (Phase I). Salix plans to develop the therapy initially for ulcerative colitis. MT1303 is also in development for multiple sclerosis and psoriasis. If successfully developed, the compound would be a non-immunogenic therapy for treating GI and other conditions which are currently treated with biologics.

NOVARTIS AG
Sandoz International GMBH
SHIONOGI & CO. LTD.

Sandoz International GmbH licensed exclusive commercialization rights in Germany, the UK, and the Netherlands to its **Shionogi & Co. Ltd.**'s *Rizmoic* (naldemedine). Shionogi retains development and manufacturing rights. (Apr.)

Rizmoic was approved in the EU just last month for opioid-induced constipation (OIC) in opioid-taking adults with non-cancer-related chronic pain. The peripherally-acting mu opioid receptor antagonist complements Sandoz's existing portfolio of thirteen opioid analgesics and will and will benefit from the German company's existing European presence. Launches in Germany and the UK are planned for this year, with an introduction in the Netherlands expected in 2020. *Rizmoic* is already sold under the *Symproic* brand in Japan and the US (by **BioDelivery Sciences**); it was cleared for marketing in both those regions in 2017.

PIERRE FABRE GROUP
PUMA BIOTECHNOLOGY INC.

Puma Biotechnology Inc. granted **Pierre Fabre Group** exclusive rights to develop and sell the EGFR inhibitor *Nerlynx* (neratinib) in Europe (excluding Russia and Ukraine), countries in North Africa, and Francophone countries of West Africa. (Apr.)

Nerlynx is marketed for the treatment of early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and is indicated for adult patients who completed adjuvant trastuzumab-based therapy less than a year prior. Puma gets $60m up front and up to $345m in regulatory and sales milestones, plus double-digit royalties. Pierre Fabre will carry out any additional necessary studies and is responsible for regulatory activities under guidelines of the EMA. Puma originally gained *Nerlynx* from Pfizer back in 2011, and has since completed development and out-licensed rights to a number of partners globally including **Specialised Therapeutics** (Southeast Asia), **Medison Pharma** (Israel), **CANbridge Life Sciences** (mainland China), **Pint Pharma** (Argentina, Brazil, Chile, Colombia, Mexico, and Latin America), and most recently **Knight Therapeutics**, for Canada under a deal penned earlier this year. The collaboration with Pierre Fabre is the largest of the *Nerlynx* deals by value, second to the agreement with CANbridge under which it received $30m up front and could see up to $225m in milestones.

RENEURON GROUP PLC
FOSUN INTERNATIONAL LTD.
Shanghai Fosun Pharmaceutical Group Co. Ltd.

ReNeuron Group PLC licensed **Shanghai Fosun Pharmaceutical Group Co. Ltd.** exclusive rights to develop, manufacture, and commercialize its CTX and human retinal precursor cells (hRPC) programs in China. (Apr.)

ReNeuron will receive $7.9m (£6m) up front, up to $7.9m in development milestones, $10.5m in regulatory milestones, and up to $78.5m in sales milestones (due at a rate of 5% of annual net profits). ReNeuron is also eligible for 12-14% in tiered sales royalties. Fosun Pharma is responsible for funding all development and commercial activities. ReNeuron will supply Fosun Pharma with the CTX and hRPC cells until technology transfer activities have been completed, after which time Fosun will take over manufacturing activities. ReNeuron's CTX cell therapy ReN001 demonstrated positive results from a Phase II trial as a treatment for patients living with chronic disability following stroke. The candidate was able to reverse the functional deficits associated with stroke disability when administered several weeks after the event in relevant preclinical models of the condition. ReNeuron's ReN003 cell therapy consists of hRPCs generated using cell expansion and selection technologies. The compound is in Phase II for retinitis pigmentosa and cone-rod dystrophy.

ROIVANT SCIENCES GMBH
Sinovant Sciences Ltd.
MEDIGENE AG
CYTOVANT SCIENCES

Roivant Sciences GmbH and its **Sinovant Sciences Ltd.** division have launched a new company named **Cytovant Sciences**, which will focus on cell therapies for the Asia market. Concurrently, Cytovant penned its first deal, licensing exclusive rights to immunotherapies from **Medigene AG**. (Apr.)

Cytovant gains exclusive rights to develop, manufacture, and sell in Greater China, South Korea, and Japan Medigene's T-cell immunotherapy targeting the New York esophageal squamous cell carcinoma 1 (NY-ESO-1) tumor antigen and also gains a dendritic cell (DC) vaccine targeting Wilms Tumor 1 (WT-1) and Preferentially expressed Antigen in Melanoma (PRAME). The partners will also work together to discover T-cell receptor (TCR) immunotherapies for two additional undisclosed targets; the TCRs will be generated by Medigene specifically for Asian patients. Under terms of the deal, Cytovant pays $10m up front and up to $1bn in development, regulatory, and sales milestones for four projects over multiple indications, plus low-double digit royalties. (*Strategic Transactions* estimates 10-29%.) It will also reimburse all of Medigene's related R&D costs. Cytovant is the sixteenth "Vant" company to be set up by Roivant Sciences. In total, the company's subsidiaries are currently working on over 35 compounds in 14 therapy areas.

SHANGHAI MIRACOGEN INC.
SYNAFFIX BV

Shanghai Miracogen Inc. licensed non-exclusive rights to **Synaffix BV**'s *GlycoConnect* and *HydraSpace* antibody-drug conjugate (ADC) technologies for use in the development of its clinical-stage cancer candidates. (Apr.)

Miracogen could hand over up to $125m in up-front and milestone payments, plus royalties. The *GlycoConnect* platform involves chemoenzymatic antibody remodeling and a proprietary metal-free click probe for site-specific conjugation, and *HydraSpace* (compatible with *GlycoConnect*) is an ADC-enhancing spacer technology comprised of a small highly-polar spacer subunit placed at distinct locations in the ADC linker payload. The licensing follows a research collaboration signed between the partners focused on a specific but undisclosed candidate. While the project for which Miracogen intends to use the licensed platforms was not revealed, the company's clinical pipeline includes compounds for colorectal, head and neck, gastric, and breast cancers, as well as non-Hodgkin's lymphoma. Earlier this year, **Mersana** took nonexclusive rights to *GlycoConnect* in a deal that could be worth up to $295m for Synaffix.

FINANCINGS

ACTINIUM PHARMACEUTICALS INC.

Actinium Pharmaceuticals Inc. (targeted cancer therapies) netted $15m through a public offering of 42.86 million common shares at $0.385. Investors also received

five-year warrants to purchase another 42.86 million common at $0.50. Proceeds will support completion of a Phase III trial with lead candidate *Iomab-B* (conditioning treatment prior to hematopoietic stem cell transplant in patients with blood cancers), and will also help the company progress a Phase I trial with its refocused CD33 program to proof-of concept and support continued development of the *Iomab-ACT* targeted lymphodepletion program for CART. (Apr.)

Investment Banks/Advisors: Maxim Group LLC; William Blair & Co.

APPLIED THERAPEUTICS INC.

Applied Therapeutics Inc. has filed for its initial public offering on the Nasdaq. (Apr.)

Investment Banks/Advisors: Citigroup Inc.; Cowen & Co. LLC; Robert W. Baird & Co. Inc.; UBS Investment Bank

ARTEAUS THERAPEUTICS LLC

Arteaus Therapeutics LLC sold Royalty Pharma all its royalty interests on future global net sales of *Emgality* (galcanezumab), a calcitonin gene-related peptide (CGRP) antagonist antibody for the prevention of migraine, for $260m. (Apr.)

Investment Banks/Advisors: Morgan Stanley & Co.

AUTOLUS LTD.

Autolus Therapeutics PLC (T-cell reprogramming for cancer treatment) netted $109m through the public sale of 4.83 million American Depositary Shares (including the overallotment; representing 4.83 million common) at $24. Offering proceeds will be combined with the company's over $200m in cash on hand to support continued project development, with the majority earmarked for continued trials of AUTO1 for adult acute lymphocytic leukemia (ALL), AUTO3 for pediatric ALL and diffuse large B-cell lymphoma (DLBCL), AUTO2 for multiple myeloma, and AUTO4 for peripheral T-cell lymphoma. (Apr.)

Investment Banks/Advisors: Goldman Sachs & Co.; Jefferies & Co. Inc.; Wells Fargo Securities LLC; William Blair & Co.

AVEO PHARMACEUTICALS INC.

Aveo Pharmaceuticals Inc. (Aveo Oncology) netted $23m through a public offering of 21.7 million common shares at $1.15. Investors also received two-year warrants to buy 21.7 million additional shares at $1.25. Funds will go towards continued development of the company's pipeline of candidates for renal, pancreatic, esophageal, and head and neck cancers, as well as acute myeloid leukemia, cachexia, and age-related macular degeneration. (Apr.)

Investment Banks/Advisors: HC Wainwright & Co.

BIODELIVERY SCIENCES INTERNATIONAL INC.

BioDelivery Sciences International Inc. netted $48m in a follow-on public offering of 10 million shares at $5. Selling stockholders sold an additional 2 million shares. In a concurrent deal worth a potential $30m, the company in-licensed US commercialization rights to **Shionogi**'s *Symproic* (naldemedine) peripherally-acting mu opioid receptor antagonist for opioid-induced constipation. (Apr.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; HC Wainwright & Co.; Roth Capital Partners; SunTrust Banks Inc.

CORTEXYME INC.

Cortexyme Inc. (diagnosis and treatment of neurodegenerative diseases) filed for its initial public offering on Nasdaq. (Apr.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Canaccord Genuity Inc.; Credit Suisse Group; JMP Securities LLC

DBV TECHNOLOGIES SA

DBV Technologies SA (immunotherapies) netted $31m through a public offering of 4.9 million American Depositary Shares (representing 2.45 million ordinary shares; includes the overallotment) at a price of $6.75 per ADS. The company concurrently sold 3.55 million ordinary shares at $13.50 (€12.02) in a related European private placement. Proceeds from both sales (together termed the "global offering") will support development and future commercialization of the *ViaSkin* Peanut epicutaneous immunotherapy for peanut allergies. (Apr.)

Investment Banks/Advisors: Citigroup Inc.; Goldman Sachs & Co.; HC Wainwright & Co.

DBV TECHNOLOGIES SA

DBV Technologies SA completed a private placement of 3.5 million ordinary shares at $13.50 (€12.02; a 75% premium) for net proceeds of $45m. The offering, to European investors, closed concurrent with a related public financing of 4.9 million American Depositary Shares (representing 1.66 million ordinary) that netted $31m. Combined proceeds from the global offering will support R&D and launch of DBV's *Viaskin* Peanut immunotherapy for peanut allergies. (Apr.)

EIGER BIOPHARMACEUTICALS INC.

Orphan drug developer **Eiger BioPharmaceuticals Inc.** netted $46.5m through a follow-on public offering of 4.5 million common shares priced at $11 each. The company plans to use the funds for clinical development of its hepatitis delta virus (HDV) programs, including moving peginterferon lambda into a registration study, and for pipeline advancement. (Apr.)

Investment Banks/Advisors: BTIG LLC; Citigroup Inc.; Jefferies & Co. Inc.; Ladenburg Thalmann & Co. Inc.; Robert W. Baird & Co. Inc.

FORTRESS BIOTECH INC.
Mustang Bio Inc.

Mustang Bio Inc. (gene and cell therapies for cancers and rare genetic diseases) entered into a $20m venture debt financing agreement with Horizon Technology Finance. The company received $15m of the loan up front and can draw down on the remaining $5m pending achievement of preset milestones. The loan accrues interest at a rate equal to 9% plus the amount by which the one-month LIBOR rate (as reported in the *WSJ*) exceeds 2.5%, and will be repaid in 42 monthly payments (18 months interest only and 24 months of principal and accrued interest). Upon the initial closing, Mustang issued Horizon ten-year warrants to purchase 288k common shares at $3.47. (Apr.)

GRITSTONE ONCOLOGY

Gritstone Oncology Inc. (developing tumor-specific immunotherapies) netted $70.3m through the public sale of 6.5 million common shares at $11.50. Proceeds will support Phase I/II studies with neoantigen-based solid tumor immunotherapies Graniteoo1 and Slateoo1; build-out of the company's manufacturing facility to internalize production of its vaccine platform; and additional R&D activities. (Apr.)

Investment Banks/Advisors: BTIG LLC; Barclays Bank PLC; Cowen & Co. LLC; Goldman Sachs & Co.

HOMOLOGY MEDICINES INC.

Genetic medicines developer **Homology Medicines Inc.** netted $117.5m in its follow-on public offering of 5.56 million common shares at $22.50. The company will use the proceeds to move its lead gene therapy program HMI102 for adults with phenylketonuria through a Phase I/II trial; to advance both HMI202 for metachromatic leukodystrophy and HMI103 for pediatric PKU through IND-enabling studies and possibly into the clinic; to move other pipeline programs through preclinical development; to further expand its intellectual property portfolio; and to potentially expand its manufacturing capacity. (Apr.)

Investment Banks/Advisors: BTIG LLC; Bank of America Merrill Lynch; Cowen & Co. LLC; HC Wainwright & Co.

HOOKIPA PHARMA INC.

Austrian firm **Hookipa Pharma Inc.** (developing vaccines for infectious diseases and cancers) netted $78.1m via its initial public offering on the Nasdaq of 6 million common shares at $14. The company planned to sell 6.67 million shares between $14 and $16. (Apr.)

Investment Banks/Advisors: Bank of

America Merrill Lynch; Kempen & Co.; RBC Capital Markets; SVB Financial Group

MILESTONE PHARMACEUTICALS INC.

Cardiovascular disease-focused **Milestone Pharmaceuticals Inc.** filed for its initial public offering. (Apr.)

Investment Banks/Advisors: Cowen & Co. LLC; Jefferies & Co. Inc.; Piper Jaffray & Co.

MOLECULIN BIOTECH INC.

Moleculin Biotech Inc. netted $14.1m through a registered direct offering of 9.375 million units priced at $1.60 (a 37% premium to the ten-day market average). Each unit consisted of one common share and one-half of a five-year warrant to purchase one common, exercisable at $1.75. Oppenheimer was the placement agent. Moleculin is developing treatments for highly resistant cancers including AML, glioblastoma, DIPG, brain melanoma, pancreatic cancer, cutaneous T-cell lymphoma, and ocular tumors, and will use the offering proceeds to support continued R&D activities and other general corporate needs. (Apr.)

Investment Banks/Advisors: Maxim Group LLC; Oppenheimer & Co. Inc.; Roth Capital Partners

NGM BIOPHARMACEUTICALS INC.

Concurrent with the completion of its initial public offering, **NGM Biopharmaceuticals Inc.** sold 4.3 million of its common shares to partner **Merck & Co. Inc.** at the IPO price of $16, for net proceeds of $61m. Under terms of their 2015 alliance centered around development of NGM's biologics that modulate pathways for metabolic regulation, Merck previously held a 15% stake in NGM; that stake has now increased to 19.99% following the IPO and private placement. (Apr.)

NGM BIOPHARMACEUTICALS INC.

NGM Biopharmaceuticals Inc. netted $99.2m in its initial public offering on the Nasdaq of 6.67 million shares at $16 each, the high end of its anticipated range. The company filed for the IPO in September 2018. (Apr.)

Investment Banks/Advisors: Citigroup Inc.; Cowen & Co. LLC; Goldman Sachs & Co.

OUTLOOK THERAPEUTICS INC.

Ophthalmic-focused **Outlook Therapeutics Inc.** (formerly Oncobiologics) netted $26.8m through a follow-on offering of 10.34 million common shares at $2.75. The company also issued 15-month warrants to purchase up to 10.34 million common shares and five-year warrants to buy another 10.34 million shares; the warrants are exercisable at $2.90 per share. Outlook will use the proceeds for Phase III development of ONS5010 for wet age-related macular degeneration, diabetic macular edema, and branch retinal vein occlusion. Additional funds will help repay $5m in outstanding principal and accrued interest on its 5% senior secured notes due June 2019. (Apr.)

Investment Banks/Advisors: Aegis Capital Corp.; Oppenheimer & Co. Inc.

PHASEBIO PHARMACEUTICALS INC.

PhaseBio Pharmaceuticals Inc. (orphan disease drug development) netted $46.5m through the public sale of 4.1 million common shares (including the overallotment) at $12. Funds will go towards continued development of PB2452 (recombinant mAb antigen-binding fragment used to reverse the antiplatelet activity of ticagrelor and stop major bleeding episodes); PB1046 (Phase IIb for pulmonary arterial hypertension); preclinical projects; and the company's ELP recombinant biopolymer technology to extend the circulating half-life of proteins and peptides and provide for sustained release of active molecules. (Apr.)

Investment Banks/Advisors: Citigroup Inc.; Cowen & Co. LLC; Needham & Co. Inc.; Stifel Nicolaus & Co. Inc.

PLURISTEM THERAPEUTICS INC.

Regenerative medicine company **Pluristem Therapeutics Inc.** netted $17.9m through a follow-on public offering of 27.1 million common shares at $0.70 each. The company also issued five-year warrants to buy up to another 27.2 million shares at an exercise price of $0.70. Pluristem concurrently netted $940k through an RDO. Proceeds from the financings will help support R&D activities. (Apr.)

Investment Banks/Advisors: HC Wainwright & Co.; Ladenburg Thalmann & Co. Inc.; LifeSci Capital LLC; Maxim Group LLC

PULMATRIX INC.

Pulmatrix Inc. (developing inhaled therapies) netted $15.3m through the upsized follow-on offering of 10.67 million common units, selling 3.3 million units (including full exercise of the overallotment) at $1.35 (each unit consists of one common share (or common stock equivalent) and one five-year warrant to purchase one share at an exercise price of $1.35) and 8.9 million pre-funded units at $1.34 (each consisting of a pre-funded warrant to purchase one common share and one common warrant to purchase one common share at an exercise price of $0.01 per share). (Apr.)

Investment Banks/Advisors: HC Wainwright & Co.

ROCKET PHARMACEUTICALS INC.

Rocket Pharmaceuticals Inc. netted $86m through a follow-on public offering of 5.18 million common shares (including full exercise of the overallotment) at $17.50 each. The company will use the proceeds for ongoing R&D of its rare disease therapies, expansion of its manufacturing capabilities, and potential licensing or acquisition opportunities. (Apr.)

Investment Banks/Advisors: Evercore Partners; Oppenheimer & Co. Inc.; SVB Financial Group; William Blair & Co.

SANGAMO THERAPEUTICS INC.

Sangamo Therapeutics Inc. (developing gene and cell therapies) netted $136.7m through a follow-on public offering of 12.65 million common shares (including full exercise of the overallotment) at $11.50 each. The company will use the proceeds for R&D activities. (Apr.)

Investment Banks/Advisors: Barclays Bank PLC; Cowen & Co. LLC; Wells Fargo Securities LLC

SYROS PHARMACEUTICALS INC.

Syros Pharmaceuticals Inc. (gene regulation research for cancer drug development) netted $66m through concurrent public offerings of common and preferred shares. The company sold 8.67 million common shares together with Class A warrants to purchase 1.95 million common for a price of $7.50 per share, and also issued 666 series A convertible preferred shares and Class A warrants for 666k common for $7,500 per series A share. In both offerings, the Class A warrants expire in three-and-one-half years and are exercisable at $8.625 per share. (Apr.)

Investment Banks/Advisors: Cowen & Co. LLC; JMP Securities LLC; Piper Jaffray & Co.; Roth Capital Partners

THERAPEUTICSMD INC.

TherapeuticsMD Inc. secured a $300m five-year term loan credit facility from TPG Sixth Street Partners. The company drew down $200m at closing, with the remainder available in two equal $50m tranches. (Apr.)

TREVI THERAPEUTICS INC.

Trevi Therapeutics Inc. (developing nalbuphine ER for pruritic and neurologically mediated conditions) filed for its initial public offering on Nasdaq with plans to sell 4.7 million shares at a $14-16 range. (Apr.)

Investment Banks/Advisors: BMO Financial Group; Leerink Partners LLC; Needham & Co. Inc.; SVB Financial Group; Stifel Nicolaus & Co. Inc.

TRICIDA INC.

Tricida Inc. netted $218m through a public offering of 6.4 million common shares (including the overallotment) at $36. The company develops renal disease therapies and will use most of the proceeds for manufacturing, post-marketing trials, and commercial expenses related to the launch of lead candidate TRC101, a non-absorbed polymer indicated for metabolic acidosis in patients with chronic kidney disease. NDA submission is planned for 2H 2019. (Apr.)

Investment Banks/Advisors: Cowen & Co. LLC; Goldman Sachs & Co.; JP Morgan Chase & Co.; Needham & Co. Inc.

TURNING POINT THERAPEUTICS INC.

Turning Point Therapeutics Inc. (oncology) netted $178m through its initial public offering of 10.64 million common shares (including the overallotment) at $18. The company had originally filed to sell 7.35 million shares at a range of $16-18. (Apr.)

Investment Banks/Advisors: Canaccord Genuity Inc.; Goldman Sachs & Co.; Leerink Partners LLC; SVB Financial Group; Wells Fargo Securities LLC

VAXART INC.

Vaxart Inc. (infectious disease vaccines) netted $8.48m through the public offering of 925,455 common shares at $1 and pre-funded warrants to purchase 8.17 million common shares at $0.9 each. The company also sold five-year common warrants to purchase up to 9.09 of common shares exercisable at $1.10. Vaxart will use the proceeds for R&D activities including a Phase I trial of its bivalent norovirus vaccines, a Phase II study with the GI.1 monovalent norovirus vaccine, and to advance its HPV candidate, in addition to manufacturing clinical supplies. (Apr.)

Investment Banks/Advisors: CIM Securities; HC Wainwright & Co.

X4 PHARMACEUTICALS INC.

X4 Pharmaceuticals Inc. (treatments for rare diseases and cancers) netted $80.2m through a public offering. The company sold 5.67 million common shares at $11, and issued pre-funded warrants to purchase 2.13mm shares at a price of $10.999 per pre-funded warrant. Investors also received five-year Class A warrants buy 3.9 million common at an exercise price of $13.20. Proceeds will enable the company to support a Phase III pivotal trial of mavorixafor in patients with WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome; begin a Phase I trial with mavorixafor for severe congenital neutropenia; initiate a Phase I/II study with mavorixafor in Waldenström macroglobulinemia; and to fund additional R&D and corporate needs. (Apr.)

Investment Banks/Advisors: Canaccord Genuity Inc.; Cowen & Co. LLC; Stifel Nicolaus & Co. Inc.

ZOSANO PHARMA CORP.

Drug delivery firm **Zosano Pharma Corp.** netted $16m through the follow-on offering of 5 million common shares at $3.29. The company will use the proceeds for R&D activities and to prepare for the potential commercialization of its Phase III migraine therapy *Qtrypta* (M207). (Apr.)

Investment Banks/Advisors: Cowen & Co. LLC

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