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R&D MEETS THE CROWDSPACE

BY WILLIAM LOONEY

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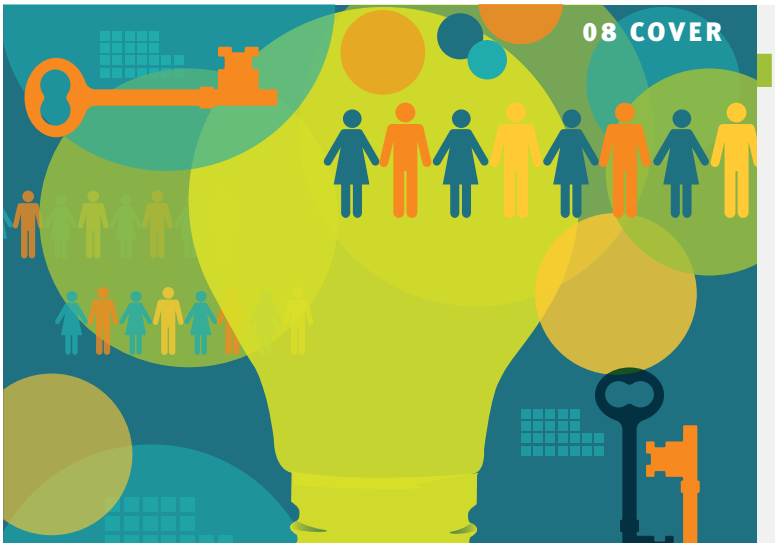

R&D Meets The Crowdscape: BioMed X Looks Outside For Insight

William Looney

It is a cliché to say that pharma science loves to collaborate – the hard thing is that leaky decision framework by which good ideas do not get executed. Germany's BioMed X "outcubator" is investing in the wisdom of the science crowd to redeploy the cognitive division of labor in preclinical research. The goal is to consistently deliver novel druggable targets that matter to markets, payers and patients.

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DEPARTMENTS

AROUND THE INDUSTRY

EXCLUSIVE ONLINE CONTENT

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COVER DESIGN: Gayle Rembold Furbert

From The Editor

LUCIE ELLIS

Welcome to the April edition of *In Vivo*. This month we have a varied collection of features spread across the life sciences sector and investigating companies both big and small. Before the Easter break and a long weekend for us all, the *In Vivo* team has been busy exploring novel approaches to treating disease, discussing big pharma corporate strategies for managing aging and changing drug portfolios, and gaining insights into new R&D models.

This month's cover story focuses on crowdsourcing as a model for research innovation. As basic research adapts to the downstream practicalities of translational medicine, more must be done to retain scientists capable of working productively in both settings. Described as an "open door to the global brain," crowdsourcing first took root in the software and high tech business; William Looney analyzes the role this approach can play in biopharma.

Also, included this month is an interview with Bayer's new head of pharma, Stefan Oelrich, who took on the role in late 2018. He explains more about Bayer's R&D restructuring plans, which will see the company focus on outsourcing and partnering for drug development. Oelrich talks about how Bayer will manage an impending patent cliff in the pharma portfolio, and where the company is placing its bets for new therapies to build a stronger company that is fit for business in the next decade.

Meanwhile, Chris Morrison takes a deep dive into the science of exosomes and their potential to solve drug delivery challenges that have limited the power and applicability of the biopharma industry's growing arsenal of therapeutic modalities. And Ashley Yeo explores the medtech sector's evolving attitude to risk in an interview with consultancy firm Technology Commercialization Group.

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Up-Front

SNAPSHOTS FROM APRIL'S CONTENT

"Our partners look to us when they want to do something different, that could be seen as too disruptive were it initiated in-house."

– Christian Tidona

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consumer care CNS
oncology
immunology
diagnostics
respiratory

Updated draft guidance released by the FDA in March 2019 on naming conventions for biologics and biosimilars has provoked strong pushback from the local and global biosimilars industry.

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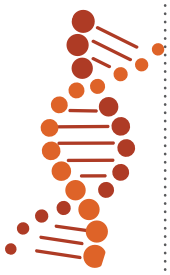

"The **role of exosomes is now well established in a number of different disease settings.** This is particularly true in cancer, where exosomes play a fundamental role in the cross talk between cancer cells and immune cells in the tumor microenvironment.

– DOUG WILLIAMS

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SCALING UP TO LAUNCH THE FIRST PRODUCT IS ONE OF THE MOST CHALLENGING TRANSITIONS FOR A BIOPHARMA ORGANIZATION.

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"Casebia is funded by two large global enterprises, but our work culture is independent and autonomous. The beauty of our model is that, in contrast to most biotech companies of our size, we don't have the distraction of constantly seeking new funds."

–Jim Burns

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Around The Industry

AI And Big Data In Focus: What Is Preventing Faster Adoption In Health Care Settings?

February's Big Data and Analytics in Healthcare forum in London was another opportunity to gauge how far the industry has come – and how far it still has to go – before digital health is an everyday reality for patients.

A high-caliber audience, assembled for Corporate Parity's second annual forum on this ground-breaking theme, broached big data's potential to deliver smarter, faster care to more people while providing improved outcomes. Delegates also assessed the current realities, including why the debate has, in fact, already lasted for several years and counting.

A microcosm of the entire ecosystem's concerns emerged in a single panel discussion chaired by HeathLynxIQ founder Marinka Natale. Do organizations really understand what is at stake with big data? That was the subtext of a panel on *Challenges In Implementing Big Data Solutions*. And yes and no was the answer to emerge.

Sutherland Healthcare Solutions' Bill Hughes spoke of the difficulties faced by big health care providers and payers. The CEO, CTO, CFO and CMO might all have a different view on what big data tools can offer, and how. Everyone has their own agenda, and getting them all on the same page and going through a group process is the challenge.

There is also confusion about what these concepts, which are more than mere technology innovations, really represent. "Large health systems don't understand what this is," said Northwell Health AVP of health care analytics Chris Hutchins. They also do not know how to use it. "Get your data organized and cleansed, so you are managing it effectively, otherwise you have no idea of the cost," he said. Stop listening to sales pitches and deal with it from a use-case perspective, he further advised.

Dipak Kalra, another panelist, explained the ostensible reluctance of organizations regarding the uptake of these new tools. These busy decision-makers, he said, are operating inside a health care machine that is relatively change-resistant. Any changes to the system normally need supplementary resources and efforts, meaning that two systems are being run in parallel for a period of time.

USE CASE VS. TECHNOLOGY

Use case is a sequence of actions, performed by one or more persons or non-human entities in or outside the system, that produce results of value to the users. In fact, the BDAH forum heard that application of analytics in an organization should almost always be driven by the use case, and rarely by the technology. The sense is that "bringing AI into a company" is the wrong approach, and rather should be "you always have to think about the use case."

And innovation is expensive, as it is selective. An organization has only finite cognitive capacity as well as limited staff capacity to embrace such changes. "It's a business model for change; and it is also – regrettably – a business-driven decision; saving lives and making patients' QoL better does not usually link to business models," said Kalra, president of the European Institute for Innovation through Health Data. But in this case, "it is true."

But there are smart ways of adopting smart technology. If a group wants to be business selective, it can bypass "the shiny new toy" and opt for more basic innovations that are already established by peers, but not in use locally. It might be more relevant to think more about how to maximize income streams or avoid costs with selective use of smart solutions. In reality, artificial intelligence (AI) is quite low down on the list of affordable, business-driven changes for health care organizations.

Almost always, the first concern among potential technology suppliers is from a regulatory standpoint. The question is usually, "What do the FDA and EU regulators think?" And it is increasingly perceived that their regulatory frameworks are too old to cope with 21st century technology. If even a minor improvement to a manufacturing process could take five years to approve, companies usually decide to stick with what they have, one BDAH delegate opined. It is a concern that neither the C-suite nor the regulators understand the language of AI.

But the regulators are making some progress, Kalra observed. The EMA is very much part of the debate about the relative benefits of randomized clinical trials versus real-world evidence. The EMA is opening its eyes to doing things differently, even if it is unsure about how to ascertain quality and trustworthiness when it comes to AI tools. "We want to establish a trustworthy approach to rating RWE, the data and algorithms … but the regulators are scared, and we've got to help them."

Another issue holding up progress is the question of where do the analytics live in an organization and who owns and drives the data? Is it IT, strategy, clinical or finance? Given the countless verticals in health care, how can organizations go as far and as deep as they need to, asked Hutchins. "Over time, the argument will settle itself over who should own it – the answer is *everyone* is responsible," he said.

The business case argument evidently holds for commercial organizations too. "For every project, we have to have hard return on investment metrics, and show where the savings are," said Hughes. But as there is no extra money around, the business equation must be met with increased revenues or decreased costs associated with projects.

In these projects, "collaboration between IT and the business experts is really the key to success," said Hughes. He added that people were more comfortable when talking about "machine learning," which is more tangible. Most of Sutherland's projects were machine-learning based, he added.

THE KEY COMPONENTS TO IMPLEMENTING AI

The influence of the human factor cannot be discounted. Reaching back into 25 years of decision-support experience, Kalra said use of mechanical, automated things, which are apparently decision-making tools, risks destabilizing the reputation of those people who currently make the decisions. People can feel threatened, and analytics is still relatively young. The risk of teams subverting or discrediting technological progress can be addressed by bringing the experts on board. "Don't have the computer replace, rather augment, the person; the goal is that they co-exist." And firing senior people to make cost-savings should not be on the agenda, he asserted.

LACK OF STANDARDS

The lack of standards for exchanging health care information electronically is a major drawback. In Hughes' view, "While there are existing standards, X12 or HL7, the more we move to something like FHIR (Fast Healthcare Interoperability Resources), the easier and cheaper it will be for everybody." FHIR is said to be the only standard that enables seamless and real-time data sharing, and it is widely thought that the FHIR standard will play a big role in next-generation interoperability.

Sharing data is another way to accelerate progress. The momentum here is really strong, Kalra ventured, noting that the FAIR (findable, accessible, interoperable, reusable) concept is gaining ground with many projects, whose managers see generic systems as a way of avoiding issues of data protection. But the bigger question is whether a single data interoperability standard is emerging. The answer is: "not really," and progress there is very slow. Kalra's advice is to pick a company that has a body of acceptance, and concentrate on putting it into practice. "From a standards point of view, make a choice and get on with it," he recommended.

THE BIOMETRICS REVOLUTION

The "elephant in the room" is the biometric revolution of mobile device data collection and sharing, Hughes observed. The whole social media revolution, and new names like Apple entering the fray, with its *Apple Watch* securing success at the FDA, and Amazon becoming a new player in health care, for instance, will give added impetus to the transformation of health care. New standards will dictate how the new sources of information can be integrated into health care data.

GOVERNANCE: THE BIGGEST CHALLENGE

But in this space, governance is the biggest challenge industry faces. The major question, as the US moves increasingly toward care coordination models, is: who really owns the data? None of the standards development organizations (SDOs) had strong patient engagement strategies, Kalra observed. There were concerns about how confident the sector could be about data that have come from third-party sources, he said, asking, "Do we know where it has come from, from whom, when it was created, and whether it is the final version?"

Increasing numbers of vendors of personal health solutions that capture patient data through apps are retaining some rights to re-exploit some of those data, anonymized. Some get paid. Patients supplying the data increasingly expect to be paid for their data (the "my data, my money" mantra). And it is an environment where a lot is heard about "democratization of data," but there is evidently a lot that can be done at the ISO and regulatory level. "We need more R&D in this area," Kalra added.

ISSUES IN INTERGRATING BIG DATA SYSTEMS AND CONCEPTS

Quite clearly, the big data, machine learning and predictive analytics space is not the straightforward journey that many would have hoped, for many reasons, including the following:

- Health care organizations often have a poor understanding of big data/AI, and their C-suites may have divergent views over how to proceed.
- There is a sub-optimal grasp of what big data quality is, how organizations should cleanse data, manage it effectively and get a good overview of associated costs.
- Change-resistance extends to fears at health care organizations that they will have to run parallel systems.
- Innovation is expensive, but the "shiny new toy" is not the only solution, given that more modest, proven solutions can also be adopted.
- Regulators, as is also the case for the C-suite, are learning as they go along regarding AI, and existing regulatory systems are likely to be outdated.
- Use of RWE and biometrics data is an inevitability, but nerves over its trustworthiness persist.
- Who owns and drives the data – is it one vertical or department, or everyone in the organization?
- The business-case and use-case approaches are the most valid ways to proceed with AI integration.
- The organization's technical experts should in no way be disenfranchized – rather, their skills should be AI-augmented.
- Sharing data appears to make sense, but it is an issue that has yet to be broached seriously.
- A single data interoperability standard has yet to emerge.
- Data governance/ownership is said to be the biggest issue, but data vendors and even patients themselves are seeking cash for their data and are adding to the blurred picture that is the backdrop for big data adoption, and use of AI and predictive analytics.

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ASHLEY YEO

FDA Sticks To Its Guns On Biosimilar Naming

Updated draft guidance released by the US Food and Drug Administration (FDA) in March 2019 on naming conventions for biologics and biosimilars has provoked a strong push-back from the local and global biosimilars industry.

FDA commissioner Scott Gottlieb summarized the key points of the guidance – which reiterates the agency's intention to use four-letter suffixes to non-proprietary names for all biosimilars, just days after the International Generic and Biosimilar medicines Association (IGBA) urged the agency to reconsider the use of a suffix-based naming system – as follows:

- The FDA no longer intends to modify the proper names of biological products that have already been licensed or approved under the Public Health Service Act without an FDA-designated suffix in their proper names.
- The FDA does not intend to apply the naming convention to the proper names of "transition" biological products, including insulin and human growth hormone. (*Also see "FDA's Gottlieb Rolls Out A Raft Of Biosimilar Reforms" - Generics Bulletin, December 14, 2018.*)
- Going forward, for interchangeable biosimilars, the FDA intends to designate a proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters.

This final point means that naming conventions for interchangeable biosimilars will be the same as those currently applied to approved biosimilars that have not received the "interchangeable" designation. Products licensed first as a biosimilar and then later granted interchangeable status will keep the same non-proprietary name plus suffix.

"Even though biosimilars have no clinically meaningful differences from the reference product," Gottlieb said, "these unique suffixes are a critical component of the FDA's ability to track adverse events to a specific biological product and manufacturer so that appropriate action can be taken when needed to protect patients." He added, "In advancing consistency in the convention for naming all newly licensed biologicals – be it originator, biosimilar or interchangeable products – we aim to mitigate the risk of false perceptions from health care providers and patients that there's a difference in the relative safety and effectiveness of these biological products based on their name."

As time goes on, and more biological products are introduced to the market with distinguishable suffixes, Gottlieb suggested that "patients and providers increasingly will understand that the suffixes reflect a consistent naming convention and are not an indicator of product quality."

NO OTHER JURISDICTION USES A SUFFIX

Reacting to the latest guidance, the IGBA reiterated that, after a recent Health Canada decision not to adopt suffixes for biological naming, "introducing a meaningless suffix is now off the table in major regulatory markets and there is no other jurisdiction, apart from the US, which has introduced a suffix." (*Also see "Canadian Decision On Biological Names Leaves US As The Outlier" - Generics Bulletin, February 19, 2019.*)

"Biosimilars sharing the same international non-proprietary name (INN) as their respective reference products is scientifically sound and consistent with the approach taken by all stringent regulatory authorities in case of manufacturing changes of biopharmaceuticals with no impact on safety and efficacy," the association insisted.

Last year, Australia's Therapeutic Goods Administration (TGA) was praised by the IGBA for its decision not to use specific identifier suffixes as part of naming conventions for biologics. *(Also see "Australia praised after rejecting biologic suffix" - Generics Bulletin, February 2, 2018.)* The World Health Organization (WHO) in 2017 suspended its proposal for a "biological qualifier" that would have applied a random four-consonant code to the non-proprietary names of both biosimilars and brand biologics. Meanwhile, Japan's approach to biosimilars uses the non-proprietary name followed by the letters "BS" – to signify "biosimilar" – and a sequential number, rather than adding a suffix to the name. And the EU – which uses a combination of INNs and brand names to identify biologics and biosimilars – "has the largest experience with biologicals, including biosimilar medicines and applied consistent regulatory science," the IGBA noted.

DEBATE IS FAR FROM OVER

However, the international association acknowledged, "the debate is far from being over in the US." Identifying biologicals by a combination of their brand name and INN had been "the universal approach" prior to the arrival on the market of biosimilars, the IGBA pointed out. "Several biologicals already shared the same INN before biosimilars market entry, and it did not raise concerns amongst the stakeholders, including the agencies."

The IGBA noted that adalimumab had seen an unprecedented synchronicity in the launch of multiple versions over a short period of time and the system was holding on. "As have the human growth hormone products and other products in the US market for many years. The naming debate only started when biosimilars started to get approved."

The association added, "While we strongly believe that the growing body of evidence in support of the safety of a shared INN and unique brand name should convince the FDA that the current naming guidance needs to be reconsidered to align with global consensus, it appears from the recently released draft guidance on biologics naming that there continues to be resistance to this approach under current agency leadership." Still the IGBA is optimistic that the recent draft guidance presents the opportunity to engage in "a constructive, fact-based discussion with the FDA to reconsider the US approach to biologics naming holistically."

Noting that the latest draft guidance was open for comment, the FDA said that "based on the comments received" it intended to ultimately issue a "revised, final version of the 2017 non-proprietary nam-

ing of biological products guidance that amends the relevant sections necessary to incorporate input we receive through this comment period."

IMBALANCE CREATES GREATER RISK

"We believe that the imbalance between suffix-based naming for originator biological products and biosimilar products currently observed in practice and proposed to be formalized in the draft guidance cannot effectively improve the US pharmacovigilance system," the IGBA stated. "In fact," the association explained, "the current imbalance creates a greater risk for pharmacovigilance errors – for example, if an adverse event (AE) related to the use of a biosimilar is recorded without the suffix, absent of other identifying information, the AE could easily be mis-attributed to the originator."

Moreover, the IGBA took issue with the FDA's decision not to retrospectively apply suffixes to older, already-approved biologics. "Retrospective application of the current US naming policy to all originator biologic products is imperative for the suffix-based system to function," the industry association insisted. "If retrospective application is considered to be too complicated and costly to implement, the suffix-based system must be removed for all biologics, including biosimilar medicines."

TOO COSTLY TO CHANGE OLD BIOLOGIC NAMES

Justifying the FDA's decision not to retrospectively apply suffixes, Gottlieb noted that the agency's 2017 guidance on biologics naming had provoked "concerns from stakeholders that one aspect of the policy – changing the names of older biologics to add suffixes – would impose substantial costs on the health care system and had the potential to create confusion that could increase risks to patients, as drug names don't often change after drugs go to market."

"After careful consideration," Gottlieb said, "the FDA has determined that the crucial public health goals of the naming policy could still be accomplished by applying the naming convention to newly licensed biological products, while avoiding the negative consequences raised by extending the naming convention to previously licensed products."

> "Retrospective application of the current US naming policy to all originator biologic products is imperative for the suffix-based system to function."
> – IGBA

To go back and change the names of previously approved products would be a costly enterprise for the health care system, he observed. Moreover, Gottlieb said, "if those costs were to be passed on to patients, that impact would run directly counter to the goals of access and affordability that underlie the biosimilars program."

"Requiring retrospective name changes would not help advance the interest of effective pharmacovigilance since these products are already generally distinguishable by their proper names," he claimed. All 17 biosimilars approved in the US to date bear a brand name, as well as their INNs plus suffixes. "The FDA has developed its naming policy with a view to the March 2020 transition, when the biosimilar and interchangeable pathway will open to additional products, such as insulin," Gottlieb added, noting that the agency was "continuing to carefully consider the application of the naming convention to vaccines."

CHANGE OF POLICY IS STILL POSSIBLE, CLAIMS IGBA

"Well-intentioned though FDA's suffix-based naming policy may be, the fact is that the current piecemeal approach has created substantial uncertainty and risk in the US health system," the IGBA summarized. "We strongly believe that given the increased risk associated with the current imbalance, the high costs, and huge challenges linked to implementation and confusion in the marketplace should provide convincing arguments to the FDA to drop the US biologic suffixes, instead of proceeding with a two-tier system that arbitrarily distinguishes certain products with suffixes."

As a trade association, the IGBA "simply continues to believe that a change of policy may still occur to align with fact-based global consensus against suffix-based naming."

LOCAL INDUSTRY ALSO UNHAPPY

Local generics and biosimilars industry body the Association for Accessible Medicines (AAM) has also voiced criticism of the latest FDA guidance. "The AAM is reviewing the FDA's new draft guidance on biosimilar naming requirements and will submit comments to the docket," it stated. However, the association made clear its belief that "the FDA's current requirement of suffixes presents a significant, artificial barrier to biosimilars that is misaligned with the agency's own biosimilars action plan and the Trump administration's commitment to lowering drug prices for America's patients."

Meanwhile, the country's Biosimilars Forum said the latest guidance represented a direct blow to biosimilars uptake in the US. "The decision abandons the retrospective addition of a suffix to origination biologics," the Biosimilars Forum observed, "leading to an unsubstantiated notion that strict pharmacovigilance is only essential for biosimilars."

"This decision will disincentivize biosimilar uptake at a time when the government should be implementing policies that incentivize the use of biosimilars, as they are one solution to help attack rising health care costs," the Biosimilars Forum insisted. To realize the potential US savings from biosimilars of "US $54bn dollars in health care costs over the next decade, will require strong policies to create a more competitive marketplace leading to increased uptake of these lower cost, life-saving treatments."

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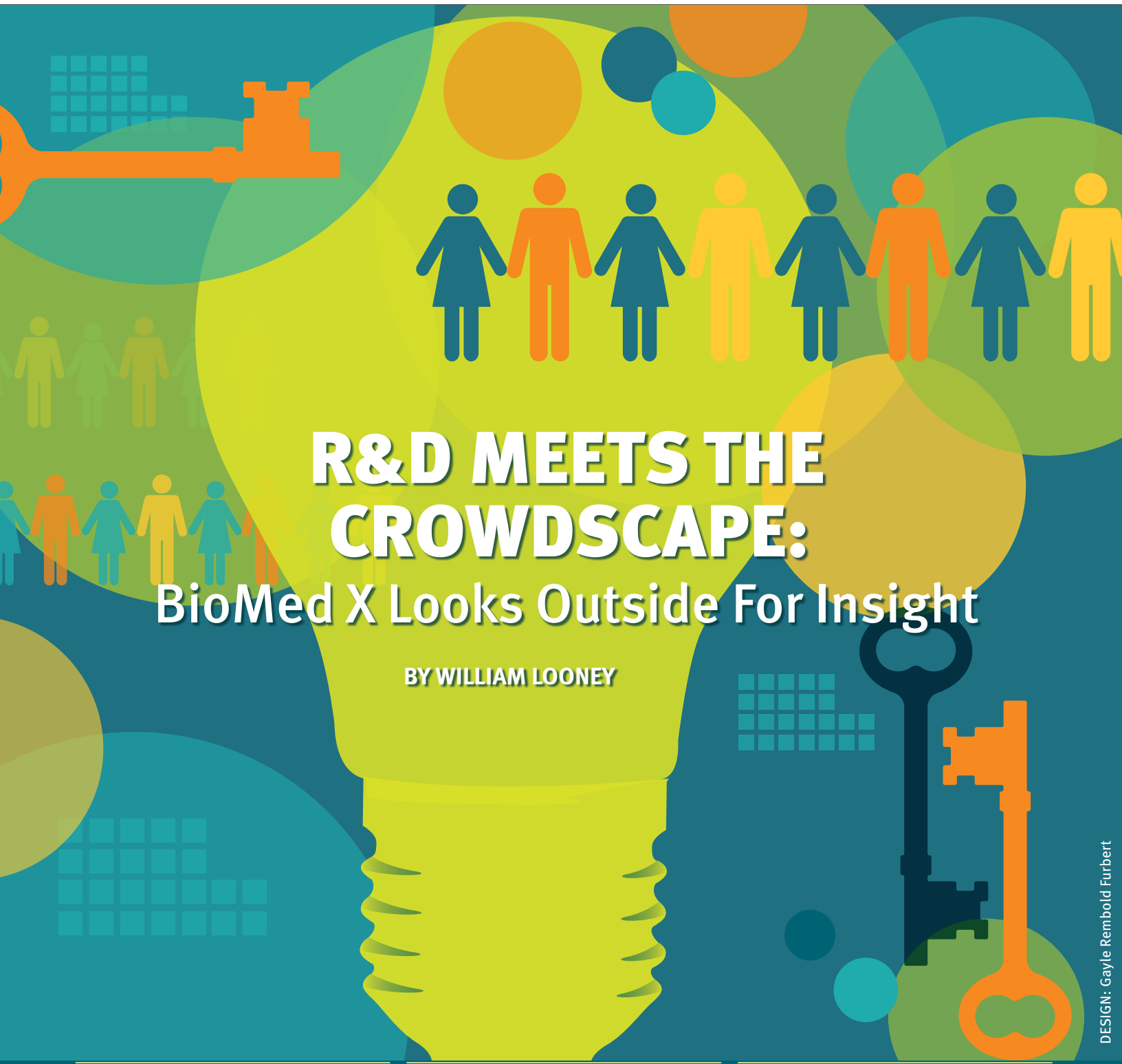
DAVID WALLACE

[Editor's note: A version of this article was first published by In Vivo's sister publication Generic's Bulletin.]



R&D MEETS THE CROWDSCAPE:

BioMed X Looks Outside For Insight

BY WILLIAM LOONEY

DESIGN: Gayle Rembold Furbert

Germany's BioMed X "outcubator" is investing in the wisdom of the science crowd to redeploy the cognitive division of labor in preclinical research. The goal is to consistently deliver novel druggable targets that matter to markets, payers and patients.

As basic research adapts to the downstream practicalities of translational medicine, more must be done to retain scientists capable of working productively in both settings.

So what? An open crowdsourcing model requires commitments to strategic discipline and operational efficiency so that the next wave of innovations is also market relevant and commercially feasible – BioMed X is a leading global advocate for this approach, but additional examples of this interdisciplinary form of biopharma engagement are needed.

IT IS A CLICHÉ TO SAY THAT PHARMA SCIENCE LOVES TO COLLABORATE – THE HARD THING IS THAT LEAKY DECISION FRAMEWORK BY WHICH GOOD IDEAS DO NOT GET EXECUTED.

Solving hard problems in biopharma usually starts like this: expert teams of specialists develop a research premise, test it in a carefully-defined cohort of patients and then validate the results using standard randomized methodologies. Failure rates are high because, at heart, drug research remains a messy exercise in improvisation. That is because we still do not know the basics of how nature uses physics to make the biology that determines individual health status.

Given the sheer number of variables in disease causation, an extended interdisciplinary approach to preclinical research may offer the best leads against today's biggest challenges in medicine. And while there is no single model that works perfectly in translating different streams of knowledge into useful innovations, the one that appears to have the most staying power due to its economy and lower risk is crowdsourcing.

Described as an "open door to the global brain," crowdsourcing first took root in the software and high tech business. The concept has evolved a bit differently within the tightly regulated world of biopharma. What crowdsourcing really means in drug R&D is mobilizing external research talent around a specific project arranged between a company and an early-stage "incubator" facility, which is in turn associated with a major academic research institute. "It is actually very grounded and results-oriented, with the added advantage of being able to generate novel science at a lower cost than doing it in-house," Dr. Ken Kaitin, Director of the Tufts University Center for the Study of Drug Development (TCSDD), told *In Vivo*.

Science Of Silos

Crowd science also appeals as a remedy for declining productivity in the biopharma pipeline, particularly for big companies with high fixed costs for R&D. Pharmaprojects' *Pharma R&D Review 2019* found that new drugs introduced by the top 25 companies in sales dropped from 18.3% of the total in 2011 to 11% in 2018; among the top 10 revenue leaders the figure was 6.45%, down from 13.2% in 2011. Small companies with one or two marketed products have leapt ahead, with portfolios bolstered by the fresh talent recruited from the endless downsizing of big pharma. Redressing this gap is a priority for the drug majors and the crowdsourced research model is touted as one solution: it replicates the freedom and flexibility of these smaller start-up enterprises without the constraints of a permanent fixed tie to one organization.

Accompanying the rise of the crowd-based model is a steep decline in funding and career opportunities in public academic research. Experienced clinicians with lab experience are being displaced and are more willing to taking assignments in the private-sector. The problem, noted Kaitin, is the difficulty in melding two different work cultures. "Integration and execution skills are the missing link in partnerships between industry and academe and can only be joined through active mentorship by the research sponsor. To work, crowd science cannot proceed *ad hoc*; having a tight decision infrastructure up and running from the start is essential to succeeding in the race to turn an idea into a product, one that fulfills a market need, beyond nice to know."

One Company's Claim To The Crowd

To explore trends and current practice in biopharma crowdsourcing, *In Vivo* spoke with a prominent leader in the space: Germany's **BioMed X Innovation Center**, established in August 2013 by some well-connected researchers in the city of Heidelberg, home to not only a world-class university and medical school, but the German Cancer Research Center (DKFZ), a public foundation; the European Molecular Biology Lab (EMBL), an

EU intergovernmental organization supported by the 28 member states; as well as 20 other local organizations focused on disease and drug research. In total, the University of Heidelberg community hosts more than 15,000 people engaged in biotech and medicine, with an additional boost from the 16,000 students enrolled in the medical school and other life science disciplines.

Dr. Christian Tidona, founder and current managing director of BioMed X, trained as a biologist and led several private biotech start-ups in the area before entering the economic development field as director of the regional Rhine Neckar Biotech Cluster (BioRN) and more recently as co-founder of Health Axis Europe, a government-backed initiative to promote the "cluster" development model around several leading university-based research centers of excellence: Heidelberg, Leuven in Belgium, Maastricht in the Netherlands, and Copenhagen in Denmark.

Tidona started by tackling that unmet need in biopharma R&D: how to tap into the global reserve of academic brainpower in a more structured way, with insights that can be applied directly to a viable research target. "The big problem we saw in crowdsourcing approaches at the time was that the big companies were good at collecting ideas but faltered in turning the inputs into projects that mesh with the decision culture and could be implemented in-house," said Tidona. "Typically, there was much difficulty in turning a contributed thesis into a commercial target, which led many executives to discount externalization as an asset in innovating R&D."

Channeling The Creatives

This was the conceptual flaw that BioMed X strives to fix. The unfiltered aggregation of novel ideas had to be redressed with some process guardrails that facilitate actionable outcomes. It starts with BioMed X signing on with a pharma company to jointly identify a tough preclinical research challenge that the company wants to solve. Only after that does the action move to the crowd, through a worldwide online call for original RFP's to address the challenge. BioMed X commonly receives several hundred RFP's, from 70 or more countries, all of which are reviewed with the company. Researchers associated with 15 to 17 of the most promising ones are selected to attend, at BioMed X's expense, a week-long "innovation boot camp" in Heidelberg. The individual candidates are arranged in five competing groups and combine their ideas into project proposals to solve the research challenge. Each group gets to pitch to a jury composed of senior R&D management of the sponsor company, after which the winning team gets a research grant to address the challenge. The grant covers four years of salaried residence for the team in Heidelberg, including access to the entire local network of scientists and its world-class physical plant.

"We are a proving ground for recruitment of the next generation of life scientists."

Christian Tidona
BioMed X

An interesting theme here is that each candidate arrives as an individual and becomes part of a team only during this week of discovery. The model allows BioMed X and the sponsors to assess team dynamics and observe how well the groups do in combining their ideas to move things forward.

"The way big pharma has traditionally looked for the brightest stars outside the private sector is like trying to find a needle in a haystack," Tidona continued. "Our global crowdsourcing approach makes the needle – unheralded young academic scientists and their ideas – come to us. We can crowdsource the best people in the various disciplines and put them to work for four years in one of the strongest biomedical research hubs in Europe." Time and a generous research budget allow these researchers full reign to unleash their creativity on a specific problem that matters to a dominant player in the industry.

BioMed X serves a larger purpose in advancing translational medicine: where basic research is redirected toward the commercialization of small molecules and biologics that matter to patients. Data is essential to this mix, but business and academia are two solitudes when it comes to using it. Academic and public research institutions generate data with an eye to getting written up in high-profile professional journals, while big pharma needs huge stores of data obtained over long periods to obtain a marketing license. That's a completely different data set, at costs that run into the tens, even hundreds of millions of

Exhibit 1
BioMed X Crowdsourcing Project Summary

TOPIC	THERAPEUTIC AREA	PHARMA SPONSOR	START DATE	END DATE	STATUS	IP TO SPONSOR
Metabolism and Signaling in Cancer	Oncology	Merck Group	8/1/2013	7/31/2017	completed	No
Selective Kinase Inhibitors	Oncology	Merck Group	8/1/2013	7/31/2016	completed	Yes
Immunosuppressive Microenvironment of Tumors	Oncology	Merck Group	3/1/2014	2/28/2018	completed	Yes
Epigenetics and COPD	Respiratory	Boehringer-Ingelheim	11/1/2015		ongoing	Yes
Nanomaterial-based Biosensors	Diagnostics	Roche	10/1/2015		ongoing	Yes
Tau-mediated Neurodegeneration in AZ	CNS	AbbVie	11/1/2015		ongoing	
Brain Microcircuits in Psychiatric Diseases	CNS	Boehringer-Ingelheim	8/1/2016		ongoing	
Oral Biofilm Disruption	Consumer Care	J&J Consumer	8/1/2016	7/31/2018	completed	Yes
DNA Damage in Cancer	Oncology	Merck Group	11/1/2016		ongoing	
Pathogen-Mediated Modulation of Innate Immunity	Immunology	Boehringer-Ingelheim	11/1/2017		ongoing	
RNA Splicing in Cancer	Oncology	Merck Group	2/1/2018		ongoing	
Rapid Identification of Auto-Antigens in Autoimmune Disease	Immunology	Janssen Pharmaceuticals	8/1/2018		ongoing	
Early Intervention in Psychiatric Disease	CNS	Boehringer-Ingelheim	Q4 2019		Call for application completed	
Intestinal Epithelial Barrier in Autoimmune diseases	Immunology	Merck Group	Q4 2019		Call for application ongoing	

dollars per therapy –at a much higher burden of risk. "In a standard bilateral collaboration, you get lots of interesting findings but what the academic partner might trumpet as a validated new drug target – because the data can be published – won't pass muster with pharma. It faces regulatory hurdles where validation requires a deeper data dive along with proof of reproducibility on the safety and efficacy of the target," Tidona said.

Project Reports

On the financial side, BioMed X is a private incubator registered in Germany as a limited liability company. It relies on income from an annual research fee covering costs for the seven staff members, physical plant and the research teams that execute the sponsors projects. These expenses are covered by the sponsor in the form of an annual project fee. At the end of the project, the sponsor has first rights to secure full ownership of the IP rights to the workstream – i.e. no future milestone or royalty payments, as is common in direct bilateral academic-industry collaborations. In return, BioMedX gets a pre-negotiated "success fee" paid by the sponsor. If the sponsor chooses to pass on the IP, then those rights are retained by BioMed X. "Transfer of IP rights to the sponsor is a very tangible marker of the practicality of our model," noted Tidona. He reports that BioMed X's first and leading big pharma partner, Merck Group KGaA, has acquired IP rights to two of the three projects it has completed to date; three others with the company are currently underway.

In the nearly six years since the launch of BioMed X, multi-platform research projects have been initiated with five big pharma, including, in addition to Merck, **AbbVie Inc.**; **Boehringer-Ingelheim GmbH**; **Janssen R&D LLC** and **J&J Consumer Health Inc.**, and **Roche Diagnostics GmbH** (*see Exhibit 1*). Most projects have a common objective: to explore a completely new field of potential drug targets; identify the most promising, within the bounds of the research protocol; and then validating these targets through *in vitro* and *in vivo* models, which, in the

best case scenario, will trigger a full-fledged drug discovery program at the sponsoring company.

"Basically, our partners look to us when they want to do something different, that could be seen as too disruptive were it initiated in-house," said Tidona. "In our first project with Boehringer-Ingelheim, we were asked to examine possible connections between epigenetics and chronic obstructive pulmonary disease (COPD). While the company was heavily invested in COPD, it did not have an active research program on epigenetics. Over four years, we succeeded in identifying several epigenetic targets that could be applied to reverse the pathology of COPD in a novel, meaningful way. It provided the independent perspective that Boehringer wanted and was also cost-effective in deciding how much resources the company wanted to devote to this new area."

In addition to specific therapy indications, BioMed X engages with companies on platform technologies and in related areas like diagnostics and materials engineering. "One of our most interesting collaborations has been with Roche, which asked us to envision a biosensor model that could incorporate sophisticated nanomaterials technology into a simple, compact and accessible diagnostic for use by physicians at the point of care. With Roche, we recruited an international team of young biomedical and nanomaterials experts who built a prototype device that was disposable, measures a variety of analytes, and could basically be read out by a personal cell phone. The Roche Diagnostics division acquired the IP package for the model, which has potential as a completely new diagnostics platform for the company. It's one of our biggest successes."

Tidona said BioMed X owed a debt to its neighbors at the Merck Group, noting that a senior executive there, vice president for innovation, Dr. Ulrich Betz, was a crucial early proponent of the crowdsourcing approach. It proved similar to Merck's Innovation Cup, a program for young academic researchers who also compete in teams for cash prizes to help advance the pipeline. To date, Merck has funded six separate BioMed X projects, mostly on challenges in the oncology space like DNA damage repair and tumor suppression.

In an interview, Betz said he coined a new term to describe the BioMed X model. "I dubbed it the 'outcubator' because it combines the creative informality of academia with the structure and discipline of a corporate R&D enterprise." Merck insisted on guidelines to ensure the company sponsor would not lose touch with the science during the four-year timeline of a typical BioMed X project. "I put forward a requirement that the sponsor appoint one of its own senior researchers to mentor the project; he or she is expected to convene at least one progress update a month with the team." Betz also insists geographic proximity has been a success factor in Merck's relationship with BioMed X, noting that the entire Heidelberg life sciences ecosystem is only a 45-minute drive from the company HQ in Darmstadt. "Human contacts are important; it's hard to complete a crowdsourcing project all virtually," he said.

One other distinctive aspect of BioMed X is its corporate research sponsors are comfortable about using the model to extend their gaze into other therapeutic areas. Examples include Merck's venture from cancer into auto-immune disorders, and Boehringer-Ingelheim's efforts beyond respiratory diseases to include novel approaches to treatment of patients with psychiatric conditions, especially adolescents. Tidona contends it's because his incubator doesn't have the restrictions commonly found in big pharma organizations, which make it difficult to take a risk and do something whimsical without fear of distraction – or censure. "Obviously we work hard to win, but I like to describe us as a 'sandbox' that softens the interface between academia and industry, combining the best of two distinct worlds. The continuing progress of BioMed X into new areas of inquiry shows that big pharma is finally opening up and embracing this new concept of seeding innovation from non-traditional sources."

Messaging The C-Suite

What is next for BioMed X? Clearly, Tidona sees himself as an advocate with designs that extend beyond just delivering R&D leaders a contracting service. Asked if he has a simple message for the C-suite, he emphasized how institutions like BioMed X can help solve the looming shortage of human capital to improve big pharma's productivity and keep operating margins in line with costs. "We are a proving ground for recruitment of the next generation of life scientists," Tidona said. "Our recruits get four years of exposure to the risk and benefits of commercially-oriented research, which stretches their learning curve to the point that most want to make the transition from pure science to the practical side, in industry. Noting that 80% of the fellows that finish their four-year stint at BioMed X move into jobs in big pharma and biotech, Tidona summarizes it this way: "our science leads not just to translational medicine, but to translational skills, writ large."

Another asset BioMed X brings to big pharma is independence. The attractiveness of an open innovation model focused on the cross-pollination of ideas would be lost if pharma companies found their innovation projects were conducted under a structure owned and controlled by a rival competitor, or even an academic institution committed to expanding its own IP portfolio. "We occupy a special position at the interface between academia and industry," Tidona said.

One option that BioMed X is avoiding – at least for the time being – is raising more capital by testing the VC market or going public. Tidona likes being a private entrepreneur and wants to maintain a pace of stable growth. The goal is to attract a more diverse array of mid-sized and smaller sponsors, as well as foundations and patient advocacy group, in addition to the big pharma firms.

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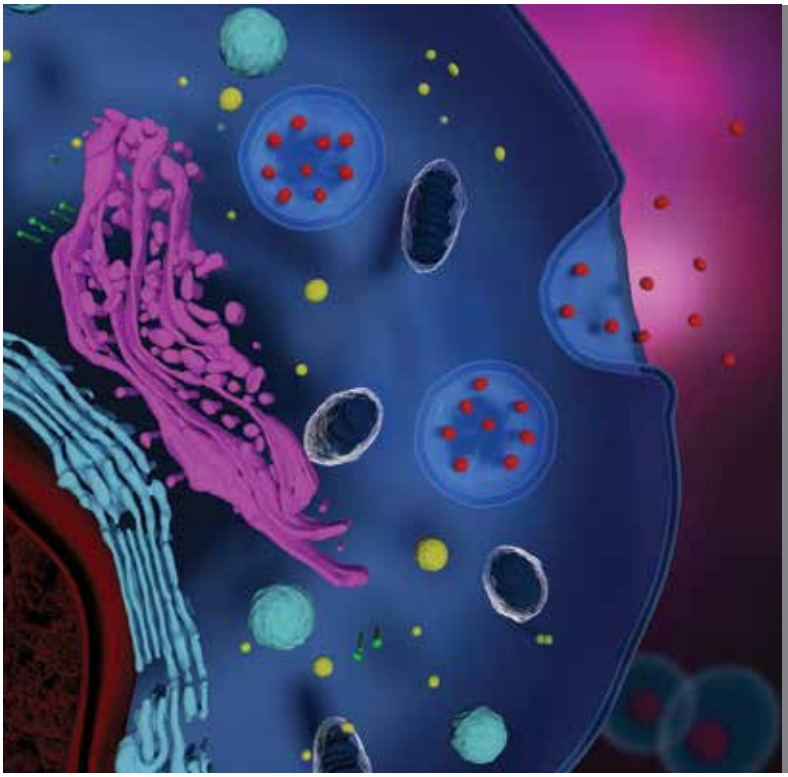

Recent excitement around exosomes underscores their potential to solve drug delivery challenges that have limited the power and applicability of the biopharma industry's growing arsenal of therapeutic modalities.

BY CHRIS MORRISON

Tiny, endogenous vesicles evolved to shuttle genetic material and biologics across long distances in the body, exosomes are beginning to attract significant venture investment and partnering attention.

Exosomes may enable efficient systemic delivery of biologics and oligonucleotides across the blood-brain barrier or into the cytoplasm of cells, or even allow for oral delivery of large molecules, extending the reach of promising molecules hamstrung by immunogenicity or delivery challenges.

Exosome therapeutics companies have seemingly learned lessons from the struggles of other platform technologies and have focused on scalable manufacturing from the outset to hit the ground running when candidates begin entering the clinic next year.

Exosomes have evolved over millennia to deliver macromolecules in their native, active forms from one cell or one tissue to another. The small lipid-membraned sacs are filled with a soup of nucleic acids and proteins: messages, signals or instructions that emerge from one cell to journey to a nearby or distant destination. Now a handful of biotech companies are repurposing exosomes as off-the-shelf treatments for various diseases, and engineering them using ligands or antibodies to route them to various tissues in the body. These exosomes can be decorated or filled, Trojan-horse style, with anything from traditional small molecules to biologics to various flavors of oligonucleotide, and sent off to hit membrane-based or even intracellular targets.

Exosomes may prove to be potent therapies – and they might solve some of the thorniest delivery problems that have limited the progress of the biopharma industry's most promising therapeutic modalities. "We're basically just hijacking a natural messaging process," said Doug Williams, CEO of the Cambridge, MA-based exosome therapeutics company **Codiak BioSciences Inc.**, founded in 2015. "This is a fascinating and ancient communication system."

In a matter of a few years, small-scale, investigator-sponsored studies of exosome therapies have been supplanted by several biotechs industrializing exosomes to create novel therapeutic platforms. Some biotechs are using exosomes that naturally contain the instructions to possibly reverse disease or injury, and already know the way there. Others are modifying exosomes derived from human cell lines to point them in the right direction – avoiding the liver, for example – to deliver a therapeutic payload like siRNA or biologics to an intracellular target. Exosomes need not come from human cells – ones found in cow milk are being tested to deliver large molecules orally to the gut. Despite these differences, the companies have plenty in common: they each emphasize the scalability of their platforms and their early focus on manufacturing, and they're attracting interest from large pharmaceutical companies and deep-pocketed investors.

Immune-Silent

Native exosomes from a variety of human cell lines and multiple species have been tested in preclinical models and small, investigator-sponsored clinical studies, and the modality appears safe. In fact, exosomes seem to be immune-silent, provoking no immune response, even on repeat dosing – an advantage over cell or gene therapies. This is true for exosomes derived from different human cell types and curiously, even exosomes derived from different species. **PureTech Health**'s platform uses purified exosomes from cow milk. The company's chief scientific officer, Joseph Bolen, noted that milk-derived exosomes do not raise the ire of the immune system because they evolved specifically over millions of years to create a tolerant environment within the GI tract of offspring. "Exosomes themselves have immunosuppressive proteins on their surfaces, and they carry within them microRNAs that have been characterized as being immunosuppressive," he said.

The first forays into using exosomes as delivery vehicles for therapeutic payloads piggybacked on the vesicles' natural tendencies and distribution profiles, said Williams. "We did a lot of biodistribution studies, and we know where unmodified exosomes distribute themselves," he explained. For example, in 2017, one of Codiak's scientific founders, Raghu Kalluri of the MD Anderson Cancer Center, showed that exosomes derived from normal fibroblast-like mesenchymal cells could deliver anti-KRAS siRNA to the pancreas in mouse models of pancreatic cancer. "We were letting the exosomes lead the way," Williams stated.

Athens, GA-based **ArunA Bio**'s lead program in stroke similarly takes advantage of the ability of exosomes to home in on particular tissues – in that case, cells in the brain. But the goal for every company in the field has always been to modify exosomes to reach tissues and cell types that aren't exosomes' natural targets. "Any cell type becomes fair game as long as you can identify a ligand or antigen on the surface of the target cell to give you that specificity for uptake," said Williams.

New Direction, New Messages

In 2011, Matthew Wood and colleagues at the University of Oxford published a paper in *Nature Biotechnology* that showed exosomes could be loaded with siRNA and directed to the brains of mice with a neuron-specific targeting ligand. "That was the first *in vivo* demonstration that exosomes could be used to target a specific tissue and deliver drugs," said Antonin de Fougerolles, CEO of Oxford-based **Evox Therapeutics Ltd.**, which was founded in 2016 by Wood and Samir el Andaloussi of the Karolinska Institute. Evox has raised nearly £46m ($60.9m), including a series B financing in September 2018, to push forward a pipeline of exosome therapeutics for rare genetic diseases, including Niemann Pick disease and other lysosomal storage disorders, the first of which will move into IND-enabling studies this year. The firm has partnerships with **Boehringer Ingelheim GmbH** and an undisclosed "top 10" biopharmaceutical company, both inked in 2017.

"We've seen a lot of interest from the pharma space," he said, which tends to fall into three areas. Companies with nucleic acid platforms want to use exosomes to deliver their therapies to tissues other than the liver. Others are eager to test exosomes to deliver large molecules across the blood-brain barrier. A third key application is the ability to deliver large molecules into the cell cytoplasm. "They're all starting to dabble in the exosomes space," added de Fougerolles, because of the advantages exosomes can offer versus man-made delivery solutions. "Some companies are already very well informed, and some are surveying the landscape and still in data-collection mode," he said.

They will have plenty of applications to choose from. "The role of exosomes is now really well established in a number of different disease settings," said Williams. "This is particularly true in cancer, where exosomes play a fundamental role in the cross talk between cancer cells and immune cells in the tumor microenvironment." Codiak has raised nearly $169m across three venture rounds since late 2015, led by founding investors ARCH Venture Partners and Flagship Pioneering. The company's lead program, exoSTING, is an engineered exosome loaded with a small-molecule STING (stimulator of interferon genes) agonist and steered toward dendritic cells with a proprietary ligand displayed on the exosome surface. Exosomes are a natural part of the process of activating the STING pathway in antigen-presenting cells, explained Williams. "Since they know how to interact with that pathway, let's see if we can make them do it better," he said, because activating the STING pathway in antigen-presenting cells within the tumor microenvironment leads to a T-cell led anti-tumor response. ExoSTING and a second Codiak candidate, Exo-IL-12, are both on track to enter clinical trials in 2020.

Pharma Interest

Exosome technologies may be reaching a tipping point where awareness among investors and potential partners translates into action. But not everyone is on board just yet. **Third Rock Ventures** partner Abbie Celniker describes the firm's interest in exosomes as "not yet." A **Merck** spokesperson described the company's business development interest as "very early."

In early January 2019, Codiak announced a deal with **Jazz Pharmaceuticals PLC** worth $56m up front and $20m in preclinical development milestones to develop five exosome therapeutics in hematologic cancers and solid tumors. The partners will be tackling five "well-validated" but heretofore undruggable targets, including NRAS and STAT3, important signaling molecules implicated in a wide variety of cancers that have so far thwarted industry's efforts to develop effective treatments. Codiak, which will develop each candidate through proof-of-concept clinical trials, is eligible to receive up to $200m in additional development, regulatory and commercial milestones per program and royalties on future sales. The deal also allows the small biotech to opt-in to co-develop and co-promote two of those candidates in the US and Canada. In addition to NRAS and STAT3, two other targets have been identified, with one to be chosen down the road. Codiak plans to develop those first four in parallel, with IND filing in two to three years.

Jazz Pharmaceuticals head of clinical

development and acting chief medical officer Allen Yang said that Codiak's leadership team and their focus on building out its manufacturing capabilities was essential as it considered a deal for exosomes technologies (Codiak says its Phase I/II good manufacturing practices (GMP) manufacturing facility will come on line during 2020). "A lot of companies have exosome technologies, but not many are invested in making the technology into a real product, into a drug?" he asked. "That's something you have to do early on." NRAS and STAT3 have been difficult to target with small molecules and traditional biologics, said Yang. But with exosomes, they can be targeted with siRNA. "We have strategically chosen these particular targets," he noted, which are difficult to target with the company's existing technology platforms.

Several large biopharma companies "have been exploring exosomes to solve the delivery problems for the payloads they have access to," said Williams. Jazz is an early adopter in that regard, he says, and a company that has been forward thinking in its use of technologies to enhance targeted therapies. The firm has experience with lipid nanoparticles, liposomes and antibody-drug conjugates, but "none of the technologies they have would allow them to go after the targets they want to hit," Williams stated.

"The field is transforming rapidly," says ArunA chief scientific officer Steve Stice, and deals such as Codiak/Jazz are generating buzz. "We would go to BIO or JP Morgan and the first thing we'd have to do is explain [to potential partners] what an exosome is. But today, big pharma knows what exosomes are. The business development people and the scientists are fully tuned in to it."

Milking It

Another early adopter is **Roche**, which in July 2018 signed on with Boston's PureTech Health in a deal worth up to $36m in up-front and preclinical milestone payments. The companies will use PureTech's milk exosome platform for oral delivery of Roche antisense oligonucleotide therapeutics (later development milestones across multiple projects could push the value of the deal to more than $1bn). In 2014, Roche acquired the oligonucleotide therapy specialist Santaris, but delivery of the company's locked nucleic acid (LNA) therapies, like that of any oligonucleotide platform, has been tricky outside the liver.

> *"The role of exosomes is now well established in a number of different disease settings. This is particularly true in cancer, where exosomes play a fundamental role in the cross talk between cancer cells and immune cells in the tumor microenvironment."*
>
> *– Doug Williams*

For now, the partners declined to disclose the therapeutic areas or specific diseases they are targeting, PureTech president Bharatt Chowrira said, noting that "the variety of epithelial cells in the small intestine lends itself to thinking in different ways" about where to focus. How the company can fine-tune its exosomes to bind those various cell types selectively would influence its thought process, he added. While Roche has exclusive access to PureTech's milk exosome platform for single-stranded antisense, the biotech can continue developing the technology for other modalities like messenger RNA (mRNA) or antibodies, says Chowrira.

PureTech's Bolen (who, like Evox's de Fougerolles, is a former CSO of the mRNA specialist Moderna Therapeutics) said that the company was looking broadly at the exosome space when it stumbled on the concept of oral exosomes derived from milk, a phenomenon he says was already relatively well described in the food and agricultural industry literature. But it was not initially on the radar for many biotechs – or PureTech's own accomplished scientific advisory board – because it wasn't published in *Nature*, *Science* or *Cell*, he joked. Exosomes themselves aren't required for nutrition, comments Bolen, but nevertheless are conserved across species, likely to help build tolerance to food as the offspring's immune system develops. "Interestingly, milk exosomes from any source are about the same – human, bovine, goat," said Bolen. "We actually learned how to milk mice. That's a process, let me tell you."

PureTech isolates cow milk exosomes through what Bolen describes as a scalable process ("our factories just eat grass," he quips), and has thoroughly characterized them in terms of their protein and lipid content, the sugars decorating those larger molecules, and the genomic sequence of anything inside. For all the similarity milk exosomes have to exosomes from other sources, it's the unique ability of milk exosomes to stand up to the rigors of the gastrointestinal tract that key PureTech's interest. "If

you take other types of exosomes that operate within the body and try to give them orally, they blow up immediately," he said. But milk exosomes have evolved to be stable during the low-pH, enzyme-rich journey through the stomach and the gut. And the opportunity to deliver fragile therapeutic modalities such as oligonucleotides or peptides or other biologics orally, within milk exosomes, would represent a significant advance. "We can load that kind of cargo and successfully deliver it orally to the GI tract," Bolen pointed out. "That's the proof-of-concept that spawned our relationship with Roche."

Natural Exosomes

Before any specialized cargo gets loaded, exosomes already have ideas of their own, which vary based on which cells they're isolated from. ArunA derives its exosomes from neural stem cells (NSCs), which it has been generating for a dozen years for use in creating research reagents for academic labs and industry. When exosomes hit industry's collective radar, said Stice, ArunA knew it already had a system for generating large numbers of them from its NSC platform. And, added Stice, those NSC-derived exosomes might have significant benefits from a safety and efficacy perspective, because they are natural products that haven't been modified, and carry some unique microRNAs involved in neural cell survival, growth and differentiation.

They're far easier to administer than NSCs themselves, which have to be injected at the site of injury and successfully take root, and can't be repeatedly administered like exosomes can. In 2016, ArunA showed that its unmodified exosomes, injected systemically, could home in on sites of neurodegeneration and neuroinjury such as stroke in multiple animal models. "We know our product will cross the blood-brain barrier at higher rates than other exosome sources and that our exosomes are taken up by tissues within the brain that are associated with motor movement and cognitive function," said Stice. ArunA's lead program in stroke should enter the clinic in 2020. The company has been primarily financed through non-dilutive sources like its NSC business, but is currently exploring venture capital financing, he says.

Down the road ArunA plans to join other exosomes companies in pursuing modified exosomes and directed delivery, though Stice declined to say what therapeutic indications they will tackle. "What we're really focused on right now is developing a way in which we can most efficiently load and deliver exosomes to the site of injury in our disease models of interest," he said, adding that the company's plan was to partner its technology this year. Pharma's immediate need is for delivery of its therapeutic cargo, Stice said, though the firm will continue to pursue the applications of its native exosomes.

All companies in the space will grapple with how best to efficiently load therapeutic cargo into exosomes in a way that's compatible with scalable manufacturing processes. And as is typical in the early days of platform technologies, the various players in the space all claim freedom to operate and strong IP positions. Codiak, for example, has patented the proprietary proteins it displays on the surface of its exosomes that help guide them to particular tissues and cell types, as well as the protein expressed in its exosomes that can drag payloads to their interiors. It has also filed extensive IP around its manufacturing processes, says Williams, and will have patent protection around individual product candidates. PureTech claims it has licensed the key patents necessary to use milk exosomes to deliver various therapeutic payloads, and ArunA says it also has freedom to operate. Evox's de Fougerolles went even further, adding that his company had a "comprehensive IP estate that gives us freedom to operate broadly in exosome therapeutics and will prove to be a significant impediment to other people in the space." Platform technology IP skirmishes are hardly unusual in biotech.

De Fougerolles, an early employee at RNA interference pioneer Alnylam, believes that exosomes are about where RNAi was 10 or 15 years ago, but are moving more quickly and on the precipice of being industrialized and advanced into human clinical studies. Native exosomes have been used in half a dozen clinical trials involving about 100 people, he says, but nobody has yet administered an engineered exosome. "We're about to start seeing a range of those engineered and drug-loaded exosomes going into man, and I think that will be a key inflection point for the field. If you're able to co-opt what nature has done that usually leads to good things," he said.

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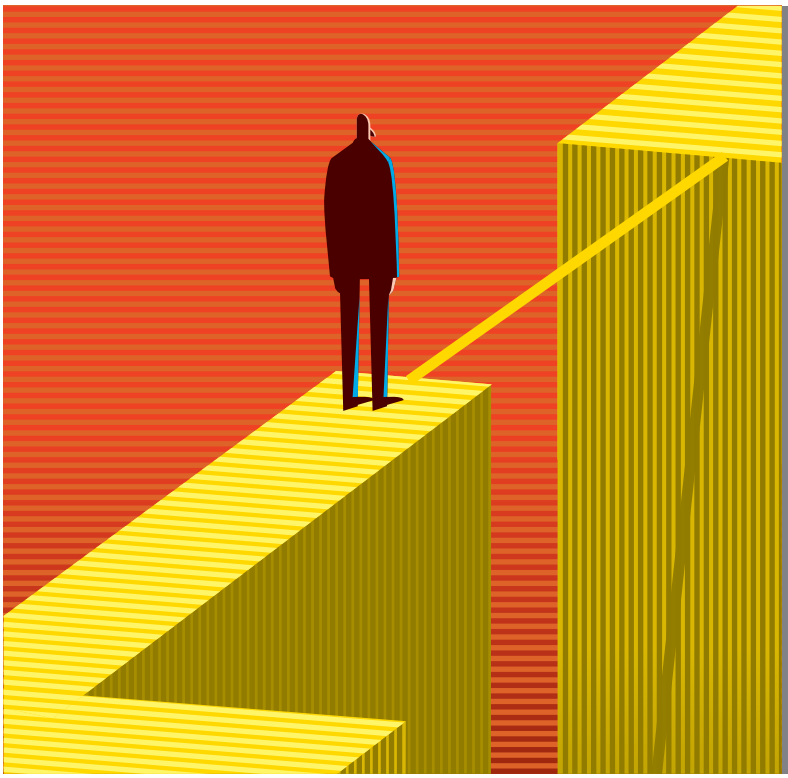
Building Bayer For The Next Decade And Navigating A Patent Cliff



As Bayer prepares for several of its key products to lose patent exclusivity in four to five years' time, *In Vivo* caught up with the company's new head of pharma, Stefan Oelrich, to hear more on his strategy for the future – especially his plans for drug R&D, collaboration and a pipeline built on external innovation.

BY LUCIE ELLIS

In late 2018, German pharma giant Bayer announced plans for a major restructure – a move that involves job cuts, plant closures and a new strategy for its pharmaceutical R&D setup.

In September 2018, Bayer introduced a new leader for the pharma business – Stefan Oelrich – who joined the company from Sanofi.

Amid all these changes, *In Vivo* explores the big pharma's strategy and forms a picture of what Bayer Pharma will look like in the next decade.

In Leverkusen, Germany, following **Bayer AG**'s full-year 2018 earnings presentation in February, *In Vivo* sat down with Stefan Oelrich to discuss his first impressions since taking on the head of pharma role last year, the company's approach to collaboration and externalization of research, and what Bayer will look like midway through the 2020s when it will hit a major patent cliff.

Bayer has around 50 projects in clinical development, with key novel compounds coming forward in the next few years that it hopes will make up for the profits soon to be lost when two of its best-selling products lose patent exclusivity. The anticoagulant *Xarelto* (rivaroxaban) and the eye drug *Eylea* (aflibercept) both face patent expirations in four to five years' time. The two products have been leading drugs in Bayer's pharma portfolio. Taking the fourth quarter of 2018 as an example, pharmaceutical sales were up 1.8% to €4.29bn ($4.7bn) and Xarelto made up €993m (+8.6%) of that figure. Eylea contributed €600m. Despite strong performances today, Bayer is expected to suffer a significant drop in revenue in 2024/2025 when both drugs will face generic competition.

Bernstein analysts expect Xarelto sales to fall to just €680m in 2030, while Eylea sales are expected to fall to €560m. Still, Bernstein analyst Wimal Kapadia recently told *In Vivo*'s sister publication *Scrip* that the products are likely to erode somewhat differently. Xarelto, a small molecule, will have multiple generics "and thus we should expect a very rapid decline, particularly in the US." Eylea, being a biologic, is likely to face less generic competition and to decline somewhat more slowly. However, Kapadia noted that growth prior to patent expiry "is also a debate given the competitive environment," with products such as possible biosimilars to Roche's Lucentis (ranibizumab) and the arrival of new drugs with different mechanisms of action for wet age-related macular degeneration and diabetic macular edema. (*Also see "Q4*

Preview: How Will Bayer Survive Patent Cliff?" - Scrip, February 13, 2019.)

Despite some concerns from analysts as to how Bayer will make up lost ground when two of its major profit makers face tough competition, Oelrich noted that Bayer still has some time to prepare its next big moves for the pharma portfolio. "At Bayer, we are in this wonderful moment in time where we still have four to five years until some of our big products go off patent, so we have time to direct other innovation modalities into the right place." He highlighted that Xarelto was the world's number four brand in the industry and the global market leader in volume terms. Despite patent expiration on the horizon, the blockbuster product could still see growth. Oelrich noted that with the launch of Xarelto in coronary artery disease (CAD) and peripheral artery disease (PAD), it is the only non-vitamin K antagonist oral anticoagulant (NOAC) available to new patient populations, which traditionally have not been treated with anticoagulants.

Changing With The Times

As part of its preparation for moving the business forward as older products lose their market power, Bayer announced in November 2018 that it would be cutting jobs and shaking things up through a company-wide restructuring. It plans to eliminate around 12,000 jobs worldwide by the end of 2021 – effecting around 10% of its total workforce. The announcement is part of a restructuring plan, designed to cut costs, streamline operations and more systematically shift pharmaceutical R&D toward external collaborations. The restructuring is the first strategic shake-up since Bayer's major acquisition of the crop science giant Monsanto completed. Bayer paid a huge $63bn to acquire the US firm, which specializes in genetically modified seeds and crop protection. The acquisition was subject to several anti-trust assessments, but it finally closed in summer 2018. However, the integration is already causing Bayer a headache, as Monsanto faces several lawsuits related to health concerns about its glyphosate-based weed-killer products.

According to several reports from late last year, of the 12,000 job cuts, half will come from corporate and supporting functions, whereas another third will be in crop science as the Monsanto integration proceeds. An additional 1,250 positions are expected to be axed in the pharma unit, and around 1,100 jobs will be cut in Bayer's consumer health division. Bayer's CEO has repeatedly declined to say how many of the reductions will be in Germany.

> *"Collaboration is a truism in life. You are never going to get the same results if you keep everything to yourself."*

Around 350 positions will be slashed at the company's factor VIII facility in Wuppertal, Germany —which Bayer will shut down to centralize all production of recombinant factor VIII in Berkeley, CA. The big pharma is also planning to cut back internal capabilities of its pharma R&D operations. Savings here will go toward additional external collaborations to boost its pipeline.

Overall, Bayer is streamlining the business around pharma, crop science and consumer health, and as a result it is weighing options to exit the animal health sector. In March 2019, Bloomberg reported that Bayer would look to auction off its animal health unit in the second quarter. The business has been valued at around $9bn and the top potential bidders are predicted to be large private equity firms. Some of the names cropping up as possible buyers are **Advent International, Blackstone Group LP**, **EQT Partners** and **Permira**.

Multiple Brains Are Better Than One

Oelrich said he was "confident" in Bayer's emerging clinical pipeline. He cited the company's current collaborations and licensing arrangements as examples of how the firm would continue to access even more innovation. And he expects this strategy to be the future for Bayer's pharma business.

Looking back, Xarelto (teamed with **Johnson & Johnson**) and Eylea (with **Regeneron Pharmaceuticals Inc.**) have proven that "we have a very good track record in partnering; we are known in the industry for this," Oelrich said. But in more recent times, the company has taken its partnering strategy into a new era, and collaboration will be the backbone of its pipeline progress.

"In my experience, collaboration is a truism in life. You are never going to get the same results if you keep everything to yourself as you would through a collaboration," Oelrich told *In Vivo*. "Just look at how science develops now; it is no longer one smart guy in a white coat in one lab in a company or university. Knowledge has spread so much, you want and need to collaborate." Bayer's model had fundamentally changed, he said. "Thirty years ago, when I was starting out in this business, when you were a young researcher you would go into academia and then your goal would be to join a large company if you wanted to do research. Today, if you are a smart researcher you stay in academia and someone is going to fund you to build your own company and see your innovation through. You don't have to go into a large company to do this."

Oelrich noted that this change in thinking had helped to speed up drug development. "This change has sped up bringing

CASEBIA COUNTS ON COLLABORATION IN ITS CLIMB TO LEADERSHIP IN GENE THERAPY


JIM BURNS

Rarely has any big pharma-biotech joint venture been so strategic – and so generous – in grafting existing expertise onto a start-up, from the ground up. And Bayer has gained some welcome protection against the distractions of the company's recent – and controversial – diversification into lines of business beyond patented medicines.

Jim Burns, CEO of **Casebia Therapeutics**, expects the company's first Investigational New Drug (IND) filing with the FDA to occur around the second quarter of 2020, most likely in the autoimmune space for IPEX, a rare mutation of the *FOXP3* gene that affects young males. Two more INDs are expected to follow in 2021, after which trials can commence, hopefully to FDA registrations by mid-decade.

Rather than attempt it on its own, Casebia plans to tackle the complexities of manufacturing at scale through well-financed partnerships with vendors with proven skills in a diversity of targeted delivery technologies.

***In Vivo:* Casebia was founded in March 2016 as a 50-50 JV between Bayer Health Care LLC and CRISPR Therapeutics AG, with a mission to commercialize CRISPR-Cas9 gene-editing therapeutics in key areas of unmet medical need. Three years in, how would you describe the state of your science thus far?**

Jim Burns: I came on board as CEO in October 2016; I was the company's third full-time employee. We started with $300 million in funding from Bayer along with licensing and IP rights from CRISPR Therapeutics covering six therapy categories: non-malignant hematology; autoimmune illnesses; blindness and retinal disorders; hearing loss; various metabolic conditions; and the cardiovascular field. Our focus is on inherited conditions that could benefit from interventions that alter or ameliorate mutations in an individual's genetic profile. In addition to the licensing head start we obtained from CRISPR Therapeutics, we have access to Bayer's substantive platform expertise in protein engineering as well as disease know-how in the areas important to us. It's a great base, and we've built on that with an IP book comprising over 40 patent applications since incorporation.

The resources from our two JV partners are bolstered by a wide-open mandate to go where the science tells us. There is nothing in our five-year financing window that requires meeting any pre-ordained development milestones. We set our own goals, the most important of which is to obtain approval from the FDA for three new IND programs by 2021, at which time we can move forward with clinical trials and eventual registration of our first commercialized therapy.

Can you clarify which of the six broad areas you are investigating appear most likely to be advanced as an IND?

We are making excellent progress in two in vivo gene-editing programs for liver diseases. A focus in the liver is using CRISPR/Cas9 to compensate for the F8 gene mutation that causes hemophilia A. The aim here is to develop a single gene-based treatment that replaces continuous bleeds with normal clotting – that long elusive cure for a condition that afflicts 150,000 patients worldwide.

Perhaps our most intensive collaboration is with the Seattle Children's Hospital, where we are working on altering T-cells to address autoimmune diseases, specifically the rare condition found in young boys called immunodysregulation polyendocrinopathy enteropathy x-linked syndrome (IPEX). The preclinical investigations center on ways gene editing can fight not only IPEX but a variety of autoimmune disorders, which occur when T-cells divert from their mission to fight disease and infection and instead start attacking healthy tissue. With Seattle Children's Hospital, we are testing how gene editing can disarm these rogue T-cells and move them back to a normal pattern of regulating the response to pathogenetic attacks on the immune system.

Based on our accelerated pace in these three areas, as well as the interesting work underway on viral vectors to modify the genes that cause retinal blindness, I believe Casebia will be ready to secure our first IND from the FDA in the second half of next year. The best probability right now is that it will be in the autoimmune space, focused on the regulatory T-cell program targeting IPEX with Seattle Children's Hospital. I expect to provide some clarity on the first IND candidate, most likely in June.

Is the Casebia business model and work culture ready for prime time?

Casebia is funded by a large global enterprise and the leading CRISPR/Cas9 technology company, but our work culture is independent and autonomous. There is no joint venture steering committee to oversee the daily routine. The beauty of our model is that, in contrast to most biotech companies of our size, we don't have the distraction of constantly seeking new funds. Nor are we shackled with a bureaucracy that penalizes mistakes and avoids risk. We expect to make mistakes. The difference is we've got the patience, the resources and the time to get it right.

Our business model is also geared to strategic collaborations that enable us to do two things: manufacture and deliver a curative gene therapy to the providers and patients who need it. Drug delivery is no longer centered on antibodies or small molecules. Every gene-based product consists of an intricate web of multiple components that must work seamlessly together – the first time and every time. An example is hemophilia A, where a gene editing platform require the use of a viral vector like the adenovirus, a lipid carrying nanoparticle, or the messenger or guide RNA to tell the nuclease where to go on the gene to make the cut.

The lesson is this: in gene editing, the process may actually be more or as important than the science behind it. And it's a great advantage to have the resources to partner with companies that already know how to assemble all these components. Right now, it's not our plan to build that kind of capacity ourselves. We will access

such expertise and spend what is required to secure it. That's an important distinction of where we stand versus our competition.

Finally, we've made good progress in building out the organization. We have 90 employees now, with colleagues based in the Cambridge, MA, headquarters and at our research center in San Francisco's Mission Bay science cluster. I've recruited key positions including a chief medical officer, head of legal, head of regulatory affairs and – looking proactively to the future – a new head of CMC development and manufacturing. This role is crucial for us as we head to the clinic and consider recruiting additional partners. I expect we will have additional news about partnering in the year ahead.

Are you considering payer/patient value propositions and other elements of the classic market access strategy to drive Casebia's future portfolio?

We're not yet ready to talk about market access. There is little discussion at the moment on pricing, and that is not uncommon in gene editing. I expect that will ratchet up once we secure the IND and move into human trials, which will of necessity involve a lot of stakeholder consultation, particularly with patients. In January, I hosted a meeting at our HQ with the parents of a child with IPEX; we've hosted visits from patients with vision disorders and hemophilia A too. These encounters are important for two reasons: it helps our researchers better understand the stakes in why they come to the lab every day; second, it allows for a different perspective than what we might normally include in our candidate development programs.

Any wild cards that might jeopardize the execution of your plans going forward?

I see the situation in gene editing as remarkably positive, even though I recognize there are still many risks and unknowns. The FDA has been progressive in its approach to our sector. The agency's leadership has sought an open dialogue, even in sensitive areas like gene editing's safety risks to patients. The stance of the European Medicines Agency (EMA) has been very welcoming as well.

IV124250 **WILLIAM LOONEY**

innovations to patients because when researchers used to enter a structure that was more constrained the work was not as fast. When we collaborate or even if we are buying a company, we want to somewhat keep them at an arm's length so that we don't lose the dynamics and the speed that make those businesses work."

Oelrich added that having credibility as a partner has been vital for Bayer's ongoing strategy for externalized R&D. "Bayer has partnered almost everything it has, we are seen as one of the top partners in the industry. It is easy to build on something where you are very credible."

Bayer has made a number of R&D deals in recent years and it has had a hand in creating new companies that are at the forefront when it comes to cell biology treatments and gene editing treatments. "We have today the nucleus to do much broader deals because we already own pieces of those companies that would allow us to extend deals if we wanted to at some point in time. Some of the products in these companies are advancing at greater speeds than we thought when we initially started the agreements," Oelrich said. "There is a biopharmaceutical evolution happening in front of our eyes. There are potentially curative approaches coming forward for some diseases that today we not only treat insufficiently, but we also are spending money on with long chronic treatments with limited benefits."

When it comes to partnering deals, Oelrich said he prefers to strike as soon as possible, to be involved from the earlier development stages. "I prefer to go as early as possible because otherwise you are taking shortcuts, and shortcuts end up costing a lot of money," he said, adding that this approach and Bayer's LEAPS program were already starting to pay off. "We hold licensing rights to some great technologies that represent great advancements in science."

Under its LEAPS program, Bayer provides the first round of funding for start-up companies to develop revolutionary science that it hopes will lead to breakthroughs both in medicine and in crop science. With the program, the company talks of "leapfrogging" the incremental steps more often seen in medicine and instead jumping ahead to curing diseases outright. LEAPS is a new iteration of the Bayer Lifescience Center, which its head of innovation, Kemal Malik, first formed in 2015, and through it Bayer has committed to fund 10 new ventures internationally, focusing on the five breakthrough technologies that have application across different therapeutic and industrial areas: DNA editing, stems cells, microbiome, RNA activation and RNA inhibition.

The initiative uses equity as a tool to set up companies that will exist externally but alongside Bayer: the new firms are given a substantial series A investment and then left to incubate the research and take it forward without interference. *(Also see "Giant LEAPS For Mankind: Bayer's Malik On Breaking The Mold In R&D" - In Vivo, April 2018.)*

Bayer will continue to move with licensing deals and partnerships to grow its pipeline, avoiding the large merger and acquisition route in biopharma, Oelrich noted. "I was eight years with another company before Bayer; when I left this company it had just come through a tough period. How did it recover? It recovered because of its ability to innovate," he said, talking about his former role at French big pharma Sanofi. "I think that is the recipe for success. If you look at some pharma companies – I won't name names – that have grown by acquiring other companies, their value over the years has not changed that much."

Focusing on recent development collaborations, Oelrich highlighted **BlueRock Therapeutics** as an example of a company developing potentially curative drugs. In December 2016, Bayer and Versant Ventures announced the launch of BlueRock, a next-generation regenerative medicine company that plans to develop best-in-class induced pluripotent stem cell (iPSC) therapies. "It is a really exciting company," Oelrich said. "Some of their projects sound more like science fiction."

Bayer and Versant each committed $225m to BlueRock, representing one of the largest-ever Series A financings for a biotech company. The funds were projected to give the start-up at least four years of runway and would allow it to advance a number of programs into the clinic, with an initial focus on cardiovascular diseases and neurodegenerative disorders.

"BlueRock has a stem cell project where they have programmed cells to be injected into the heart tissue and regrow you heart.

BLUEROCK THERAPEUTICS: SIZING UP THE REGENERATIVE POWER OF CELLS

EMILE NUWAYSIR

Bayer's novel 2016 joint venture with the venture capital group Versant Ventures has spawned something like a big pharma, new science start-up, with an open mandate to disrupt drug development through generous endowments in the scarce commodities of freedom, time and patience. *In Vivo* talks to the CEO of BlueRock Therapeutics, Emile Nuwaysir, the exemplar of this new approach, which Bayer is trusting to strengthen its cardiovascular and neurodegenerative portfolio.

***In Vivo*: BlueRock has a business proposition founded on the disruptive therapeutic potential of an artificially engineered cell. Has the science behind induced pluripotent stem cells changed in the three years since Bayer and Versant Ventures helped launch you as a startup? Does the clinical – and commercial – rationale for your platform technology remain compelling?**

Emile Nuwaysir: The idea of an engineered cell has proven to be one of the most valuable new approaches to medicine. CAR-T is a leading example of what no small molecule or biologic can do for patients. Industrializing controlled interactions between genes and the cell will have applications in all areas of medicine. Today, however, the only space where it has been enabled is in oncology. This is going to change dramatically in the next few years, and BlueRock intends to be in the vanguard.

The challenge is that, as we come to understand the treatment potential of cell therapy, progress is limited by the acceptability of high-quality cells required to manufacture a therapeutic response. We are still living with a transplant modality, where you take human cells out of the body, engineer a change and then return those harvested cells to the individual. The approach is hard to scale and is inherently limiting. Our differentiating solution is to replace the transplant paradigm with a biologic paradigm. BlueRock's proprietary platform, CELL+GENE, is a process that creates a master cell bank capable of virtually unlimited expansion into any cell type in the body. The technology is off-the-shelf, cells can be manufactured in advance and in large quantities, and quality can be inventoried and controlled, just like any biologic drug.

Overall, the approach is transformative because it solves most of the current replication and manufacturing constraints, conceivably making engineered cell therapy available to millions of new patients with any number of conditions. The regenerative medicine field is moving steadily in this direction, toward a biologic rather than a transplant/harvesting approach. In the next few years, significant amounts of investment capital will be moving this way, and our intent is to have BlueRock's pioneering platform well out in front of the competition.

How is the pipeline progressing – any movement in sight beyond the preclinical stage?

We have active programs in three areas: neurology, cardiology and immunology. Our overall focus is on degenerative conditions characterized by significant unmet need. In neurology we have four programs underway, the most advanced is a first-in-class therapy to restore dopaminergic neuron cells to the mid-brains of Parkinson's disease patients to potentially restore the motor control loss experienced by these patients. We expect an FDA decision on an IND sometime this year and are presently in discussions with the FDA on the timing of our first trial. Another part of our neurology program focuses on microglial cells, the macrophage agents in the brain responsible for the immunity defense of the entire CNS. The microglial is an enormously powerful cell, and we already possess the ability to genetically engineer and manufacture them utilizing our CELL+GENE platform.

In the cardiac space, our target is heart failure, which affects 34 million people worldwide – the greatest single unmet need in human health, for which contemporary medicine has no answer. There is proof-of-concept in non-human primates that after an induced heart attack, engineered cardiomyocyte cells can be injected to reverse the ejection fraction cell deficit in the left ventricle – essentially reversing the effects of cell death in the heart muscle.

Can you describe BlueRock's strategy on business development – how important are external partnerships in maximizing the potential of your CELL+GENE platform?

Our vision as an enterprise requires us to be ambitious across the board. When we think about the ideal partner, we look for organizations that can help us push the boundaries around engineered cell therapies to address unmet medical needs in our three therapeutic areas of focus. Our platform is transformational, not incremental; our partners should think precisely the same way. A relevant example is the partnership we signed recently with Editas Medicine Inc., a leading CRISPR genome editing company whose platform complements BlueRock's expertise in pluripotent stem cell technologies. This combined skillset will be directed to expanding opportunities for engineered, differentiated, off-the-shelf medicines in our two companies' specific areas of focus: solid tumors and blood-based cancers, for Editas; and neurology, cardiology and immunology, for BlueRock.

Given that you reference the Editas deal as a precedent-setter, what will the initial phase of this partnership look like?

Our collaboration will proceed on two fronts. First is cross-licensing, the transfer of IP rights and know-how to enable the resolution of challenges in building competencies and scale in our respective fields. Second, BlueRock and Editas will work together to generate allogeneic pluripotent matched cell banks that are optimized for immune protection to reduce rejection risks. There is a lot of excitement about the potential of this relationship.

Human capital is critical in an emerging field like cell and gene therapy, where the knowledge bank is often overdrawn. How is BlueRock securing its future on the organization and management front?

We are on a growth spurt in recruiting new talent. We now have a team based in New York, in addition to our HQ in Cambridge, MA, and facilities Toronto, Canada. In total, we have about 100 colleagues on staff now – doubling down in the last year. We've made some big commitments to Toronto, where we have a partnership with the McEwen Stem Cell Institute along with a pilot good manufacturing practice (GMP) qualified facility. We've also filled out our senior management team with some spectacular recruits. The most recent is Dr. Joachim Fruebis, as chief development officer. He will build our clinical development group and comes from Bioverativ (now Sanofi), where he executed a complex series of trials in just one year. That track record will prove useful as we launch what I expect will be multiple trials after the turn of the decade.

What's on your list to have accomplished as CEO by the end of 2020?

I have three goals. First, building on the anticipated FDA approval later this year of an IND for our native cell replacement program for Parkinson's disease, we will be deep in our human clinical trial to demonstrate how we can reverse neuron cell degeneration and restore motor control among enrolled patients. Next, we will be expanding capabilities to develop our portfolio and meet commercialization targets. That will include having a top-class clinical development team in place to handle multiple trials and establish proof-of-concept for all our pipeline candidates, with peer-reviewed publication of relevant studies. Third, I hope to push the boundaries on our approach to partnerships, with more emphasis on the kind of strategic cross-licensing pact that we just agreed with Editas Medicine. And while our finances are strong, I would not rule out larger co-development deals as our technology and assets move closer to the market.

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Heart disease remains the number-one killer in the world. While we as an industry are treating this with good things, including products in Bayer's own portfolio, developments are happening right now that will completely change how pharma works in this space. I am extremely proud to see that Bayer is very strong here," Oelrich noted. He added that breakthrough science such as cell and gene therapy, in connection with digitalization of the life science sector, "will have a major impact across the entire value chain of our industry." The pharma industry is experiencing changes that will be disruptive to the discovery and development of therapies and cures; disruptive to industry structure and the roles of different players; and disruptive to the way patients manage their own care and the way care is delivered from ability to predict, diagnose, personalize, and monitor care. "Looking at cell and gene therapy in this context, it represents one of the scientific advancements that is set to revolutionize how we will treat diseases in the future," Oelrich said. Along these lines, in 2016 Bayer was also involved in the creation of a new biotech in the CRISPR gene editing space. In December 2015, Bayer and **CRISPR Therapeutics** agreed to form a joint venture to discover, develop and commercialize new breakthrough therapeutics to cure blood disorders, blindness and congenital heart disease. The two parties formally closed the transaction in the first quarter of the following year – launching **Casebia Therapeutics.** Casebia has access to gene editing technology from CRISPR Therapeutics in specific disease areas, as well as access to protein engineering expertise and relevant disease know-how through Bayer. Casebia, which is focused on using gene editing technologies to develop treatments for diseases by the editing of somatic cells, has a pipeline of preclinical assets across four key therapy areas.

Implementing Change

Oelrich joined Bayer from **Sanofi**, where he was previously responsible for the global diabetes and cardiovascular business. He replaced Bayer's former pharma chief, Dieter Weinand, who ironically made a move to Sanofi.

Oelrich said that the business culture at Bayer was the biggest difference he had noticed when moving from one European pharma giant to another. Although the strategies are different, the challenges are the same. "You find capable people at all levels in all companies and that hasn't changed," he said. "I liked working for my previous company and I love working here. The conditions to being successful are equal everywhere; what can differ are the goals you set and the strategies you use to get there."

When considering the most meaningful change he has affected so far as Bayer's head of pharma, Oelrich said, "What I am aiming for, and I hope it shows, is that I remain very visible and I make people participate. I think I have brought with me a different communication style into the company and the feedback I am getting is very positive about that."

He added that having the right culture is essential to getting the most out of colleagues. "If you have a smile on your face when doing your work, you will achieve different results. That is something I try to bring to the company every day and I am seeing that it works; I try to empower my teams." Oelrich said this would be achieved by ensuring "we have the right people on board and that we are all working toward the same golden strategy." While there is "always a financial goal and a clear strategy to go with that, I am trying to lift it slightly on the qualitative side to have a clear vision of what we want to be," he said. "So, what does Bayer want to be in 10 years' time? You can see a glimpse of the future Bayer as we look at emerging portfolios."

Oelrich added, "We are at the crossroads when it comes to our innovation strategy as we previously relied more on our in-house technology. For example, Xarelto, the last big, big product, came from our own labs. But innovation is moving out of the labs of big companies and into the labs of start-ups. We are responding to the trend … As we have indicated, we will have fewer Bayer researchers three years from now, but we will have more researchers working with Bayer than we have now. We are taking a piece of our R&D budget and dedicating it to external research because that is where innovation is coming from."

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Medtech Innovators Must Find The Right Problems To Solve

In the world of medtech innovation, investment and market access, commentators are seeing a maturing attitude to risk, more readiness to address workflows and greater awareness of being on the ball in a regulatory sense. Senior executives from consultancy firm Technology Commercialization Group (TCG) give *In Vivo* their take on what is behind these changes.

BY ASHLEY YEO

Early-stage funding for medtech companies is more common than it has been in recent years, and is coming from a wider variety of investors and funders, pointing to a greater level of investor sophistication.

Regulatory compliance is ever a challenge, but gaining higher priority for medtechs are securing reimbursement and insurance coverage, and developing reliable business models – particularly in ehealth, digital health and mobile health.

So what? Companies increasingly understand the operational aspects of their product or service, which not only helps to de-risk early investment, but shows they know where it fits in the clinical workflow, that it solves a clinical problem and delivers economic value.

It is often hard to be heard above the general hubbub of medtech business in action – the soundtrack to the annual Medica event – anywhere in the vast Düsseldorf exhibition arena. But over at the North Carolina stand at Medica 2018, the Technology Commercialization Group's take on current realities and future trends in global medtech adoption were coming over clear as a bell.

TCG executives Dean Gray and Reinhard Merz, along with Russ King, president of TCG partner company **Methodsense Inc.**, were in agreement that there now seems to be more money available for early-stage projects. Gray said, "From what I have seen over the couple of years in the US, money for early- and growth-stage companies is coming not just from traditional venture capital or private equity sources, but also from angel investors, family offices and recently Asia."

In addition, capital medical equipment companies, which are always challenged when trying to attract investment (most investors are challenged by capital goods business models) are also getting more attention from family-owned investment offices in the US, which are showing increasing levels of investor sophistication. "They are making more investments at early stages, which is very encouraging for these capital equipment companies," said Gray, who is focused on medical devices, diagnostic imaging and digital health.

Why is this change evident? There are more sources of early-stage funding than there were five or 10 years ago. Angel groups are more prevalent in medtech, and non-dilutive funding has become a bigger source for start-ups. These include the National Institutes of Health (NIH's) Small Business Innovation Research (SBIR) fund (with the Small Business Technology Transfer program, known as America's Seed Fund) to help companies get through the earlier stages of product development to commercialization. These are very important programs, especially for university spin-outs – but also for non-academic spin-outs. In

fiscal 2018, SBIR and STTR invested over $1bn in health and life sciences companies, a key objective being to translate promising technologies to the private sector.

Changes Apparent In Pattern Of Investments

Medtech areas of greatest interest for investors remain cardiology, diabetes and regenerative medicine – "the usual suspects." Non-traditional life sciences investors are increasingly aware of the broader issues in medtech, and of newer technology developments. Digital health, for instance, has encouraged investors to become more active in medtech. Indeed, the tech part of the equation is both compelling and unstoppable. Digital health ideas often originate from non-life sciences individuals and organizations. "They don't have the clinical background, but they've come up with a cool concept," said Gray. And tech solutions to clinical problems can be a compelling notion, and help bring new investors into the digital health space.

Investors from outside the US – from China and also Korea, for example – have lately been more active in investing earlier in life sciences generally. It has been a feature of many partnering meetings for medtechs, in and outside the US, that Chinese VCs have a large presence, either formally or informally. But the US-China tariffs standoff has changed that a little in recent months. Until mid-June 2018, China's investment progress vis-à-vis US medtech start-ups was "going fine," but lately many Chinese companies have come under pressure to ensure cash does not go into the US. This has made it difficult for companies funded out of China to move forward in the US market.

Korean investors remain active in the US market, and indeed, several TCG client companies have Korean capital invested. They tend to be "very selective" investors, but have a deep financial commitment. They are careful to ensure that companies are properly funded and have the right resources to expand globally. "But when they do get on the map, they are solidly on the map," said Gray.

He reiterated that there is enhanced investment from accredited private individuals, angel investors and even health-care system corporate VCs and other institutions, who are getting more adventurous with earlier-stage companies. At one time, companies seeking capital were required to have a product cleared or approved for the market or to be generating revenue: an investment candidate company was one that was actually acquiring some market share. But that's changed, and so has the presence of family-owned investment offices.

> *"Some standards fall under the radar screen for much of the industry, "but they chew up cash flow very quickly."*
>
> *– Russ King*

Economic Issues Dominate Thoughts And Planning

Regulatory is no longer the biggest issue in getting onto the market; now it is reimbursement for many companies. "Some of the recent US medical device regulatory reforms have been encouraging for medtech companies; but reimbursement and insurance coverage, and developing a reliable business model, particularly in ehealth, digital health and mobile health – these are economic issues that are occupying more thinking time and requiring more effort to resolve than historically has been the case," noted King.

King also sees the attention paid to regulatory affairs starting earlier and earlier in the planning, and often at the very beginning of a company's life cycle. Methodsense is a global regulatory affairs and quality assurance consultancy that helps companies with FDA and other regulatory agency processes to obtain market entry for medical device products. Early regulatory attention on the part of manufacturers is, in many respects "a critical consideration or even a determinative consideration on capitalization," said King. And it's as much a factor in the US as globally. "These early-stage concerns speak to the knowledge of the investor population. Investors want to qualify an investment by assessing more thoroughly regulatory risks, including the risk classification of the product, the kinds of testing required for market entry and, the biggest risk: whether a product requires a clinical trial," he added.

EU medical device manufacturing companies are currently experiencing a great deal of change with the forthcoming Medical Device Regulation (MDR), ISO 13485:2016 and the reshaping of other standards, IEC 60601 on EMC testing, for instance. "They fall under the radar screen for much of the industry, but they chew up cash flow very quickly," said King. In short, the pressure EU regulators are putting on medtech companies is only increasing.

In the US, the FDA is driving to simplify matters in an ever-more-complex regulatory world. Its Breakthrough Designation is a welcome change, but Gray cautioned that "no FDA shortcut, in the end, makes it less expensive." FDA shortcuts tend to mean "pay later." But crucially, it's all about getting to market, and breakthrough medical technology and digital solutions solve certain problems.

But in summary, while still difficult, the transactional challenge in getting product clearances or approvals is perceived to be less of an issue. By contrast, reimbursement brings with it a relatively greater sense of challenge. "While the transactional nature of regulatory isn't necessarily any less challenging, the 'pain' is now more on the reimbursement side," said Gray.

Viable Business Models

The acknowledgement by companies of the need to better understand the markets they are entering, and specifically the clinical problems they are solving, while also confirming that people are willing to pay for the technology, is another factor in the maturing of players in the medtech sector. This, along with the trend to earlier-stage investment (see above), is the standout feature in today's evolving medtech ecosystem.

Companies are now aware of the need

for an economic – or business – model that shows who will make money with the device, and the nature of the insurance and reimbursement landscape. It's not a new consideration – and neither is regulatory – but it is now being factored in more. "It is absolutely critical that you have a viable business model, and that you are able to effectively argue for that model," stated stated King.

This is where value-based health care models come into play. VBHC must have a global outlook, and not just in geographic terms, but from the lab to the point of sale, to postmarket and to product improvements down the road, said Merz, adding, "Our business model as a consulting firm is to have an impact on the business goals of the company, and not in a transactional way." Merz is TCG's European lead on medical devices, pharma and biotech.

Workflow Considerations

Clinical/economic considerations are yet another key area. "Understanding the operational aspects of your product or service is important; it helps to further de-risk early investment," said Gray. Solving clinical problems and delivering economic value is a realizable goal, "but how does this product or service fit into the clinical workflow?" Does it make things easier, faster, better? "Emerging companies – and products – can easily be killed by that problem." Understanding a product's fit with clinical workflow, and how it affects overall quality of care, is an increasingly important factor to consider early in the product development process. "Founders and executives who address workflow, along with the usual clinical/economic value, regulatory and reimbursement considerations, enhance the perceived value of their product with both customers and investors. This may account for how the capital is moving backwards in the cycle," Gray suggested.

The Evolving Tech Landscape

The current top talking point is artificial intelligence: "Everyone wants an AI product – all you need is developers in the back room – but lots of them!" quipped King. "But it's got to solve the right problem." In fact, this is a challenge more broadly: many AI-driven projects and companies are carried along by the technical capability of what their algorithm platform can do. It may be deep – or machine – learning, but they haven't always started thinking about what the platform can do for users in a busy clinical setting. "Is it solving the right problems in a practical way, operationally?," asked Gray.

The big data and predictive analytics approach is happening in radiology already. The direction that medtech business is taking will lead to both market disruption and business tie-ups. "It's a real opportunity in health care: can we leverage that information for predictive purposes?"

Does TCG get a sense that major medtech companies, the Medtronics and the J&Js, are worried? Data technology companies' perspectives on these problems are different than those of traditional medtechs, the group noted. Medtechs are keenly processing what's going on, recognizing that they are behind the tech companies in terms of the technical capabilities of AI. But it is unlikely that tech companies will be solely driving the dialogue.

"Google and Apple are going to help us understand experiences," said King. While the major medtechs will solve different kinds of problems, the big-tech perspective is to look at pattern recognition from actions, events and outcomes, and to devise patient-centric, or process-centric, solutions in the hospital, or more broadly, in the entire continuum of patient care. But there will be more plug-ins and digital surgery partnerships along the way featuring the big players.

The big medtechs should be thinking about how Google and Apple can offer insights into the potential for product solutions based on patient characteristics. Paying for these services – how, when and at what level – is still an open book, but the guiding notion is that data prove the cause-and-effect relationship.

And procedure-specific reimbursement is just one path to revenues – there are others, in Gray's view. "The idea is that we may avoid a bigger cost problem by intervening now," he said. Using data to improve the overall quality of patient care may even be a bigger opportunity. Data analytics can help providers and hospitals, for example, better understand bottlenecks and barriers to achieving their quality goals in a value-based care setting. "Improved care is great for patients, of course, but it also has economic value to health care systems. It better enables them to achieve their desired reimbursement levels linked to quality goals."

There will be winners and losers in this unfolding scenario, but identifying who these will be is not straightforward or simple. "The issues will be different for every single company and product, and it's hard to generalize, as every company has its own formula and way of fitting into the ecosystem," said King. "What will always kill a company is being undercapitalized for what it needs to do. If that is the case, it's going to fail."

Big Questions For Medtechs

Many digital health companies are focused on technology, not the clinical problem. But being very specific about clinical problems is more important than ever. Gray says the biggest questions of all remain: "What's the problem? What's the problem? And what's the problem?" But just behind that are other vital questions, principally, does the solution make sense to clinicians? Do clinicians think it's a problem too? Is it a problem worth solving? And who will pay for it?

Answering these questions, in TCG's world, is increasingly important for success in medtech.

IV124247

Comments:
Email the author: *Ashley.Yeo@Informa.com*

WHAT'S THE PROBLEM?

Identifying realistic objectives is the key to a successful transaction, says TCG, whose remit is focused on assisting clients in defining their product's clinical and economic value proposition, and developing a viable business model that provides realizable value to all stakeholders. This includes finding the key partners, structuring deals that meet mutual needs and managing negotiations, as show in these case studies. The Raleigh, NC, and Heidelberg, Germany-based TCG partners with New York specialty investment banking firm Daybreak Capital Partners.

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Scaling Up For First Product Launch: Seven Hazards To Avoid

As the margin for error in the drug launch cycle continues to erode, emerging biopharma companies face a growing urgency to double down on scaling up for that first launch.

BY PIERRE JACQUET, PETER ROSENORN AND ADITYA NATARAJAN

Scaling up to launch the first product is one of the most challenging transitions for a biopharma organization as the leadership team prepares to grow an R&D-focused company with 30 to 70 employees into a multidimensional organization often at least three to five times larger, usually adding new functions, sites and geographies. Based on its extensive contacts and research with biopharma strategy and operational leaders, L.E.K. Consulting has identified seven hazards that could derail a strong first launch, for instance:

Time and again, one of the most important lessons we have learned is to start cross-functional launch planning and readiness activities early, preferably up to three years before launch.

In addition to the many unexpected turns required to adapt in a fast-changing marketplace, there are multiple decisions that must be made to successfully move the launch process forward. These include deciding the level of retained ownership of the first product in each geography, identifying the optimal commercial model for the product, and developing the underlying enterprise model that enables

Exhibit 1

Scaling Up for First Launch: Flashpoints To Address In Customer-Facing Organizations

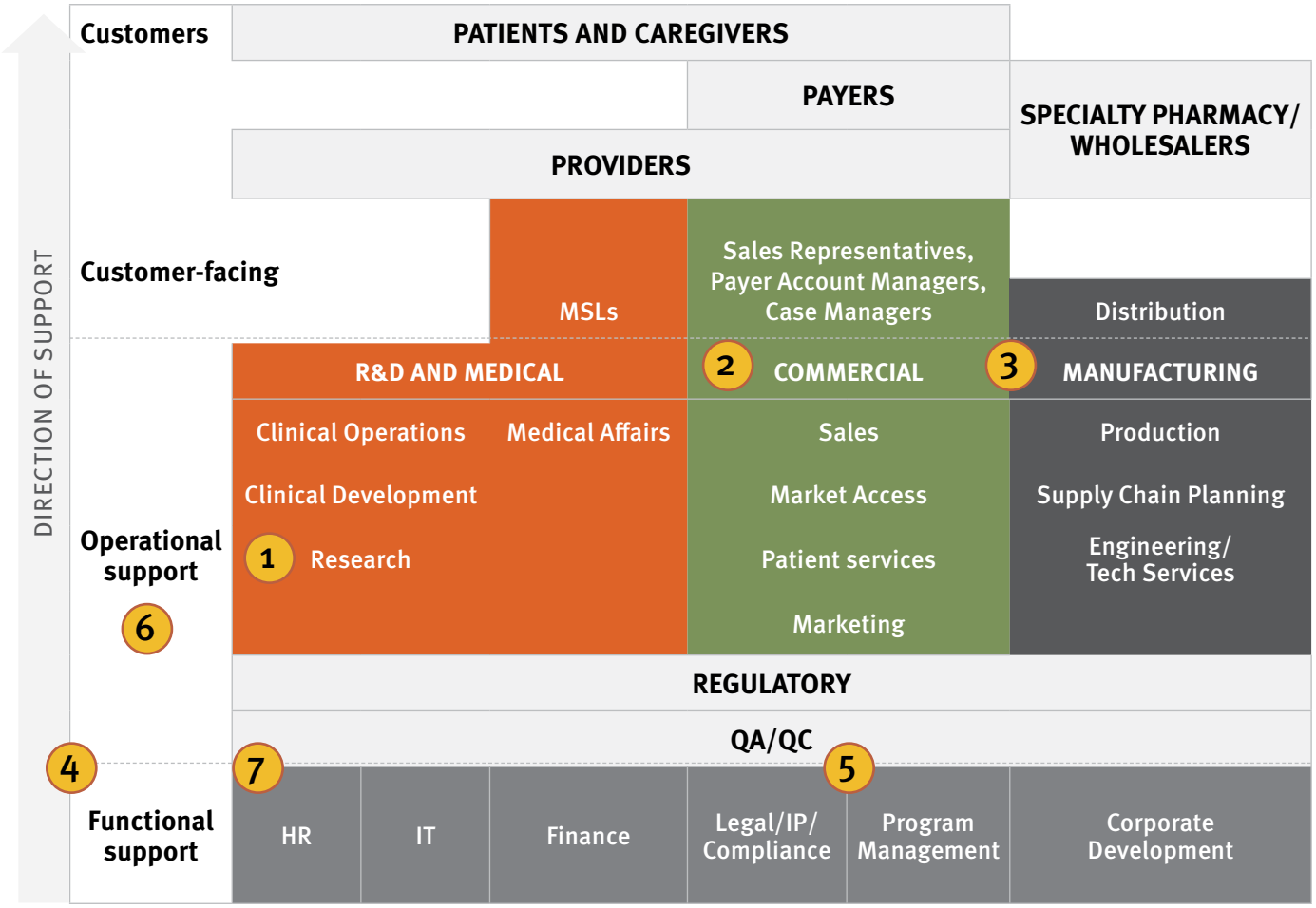
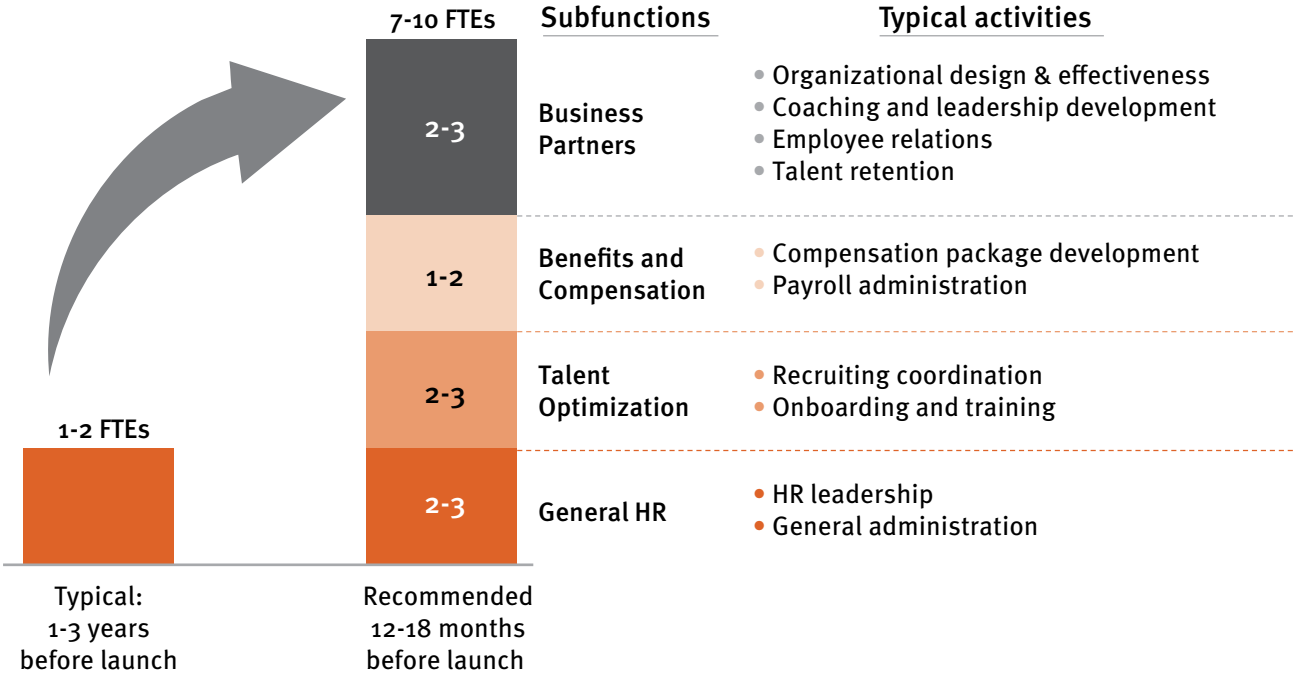


Exhibit 2

Example Of Required Pre-Launch Expansion In Back Office Functions: Human Resources



customer-facing functions to build and execute the launch plan, while simultaneously continuing R&D expansion.

A key part of a successful launch is a well-prepared organization, and in this article, we draw upon L.E.K. Consulting's experience working with biopharma companies navigating this critical transition to highlight seven scale-up hazards that executives should avoid as they prepare for launch. We indicate where they are most relevant within the customer-facing operating model, and we close with a set of key questions that management can use to self-assess whether their organization's scale-up activities are on track.

To prepare for a successful launch, emerging biopharma companies need to acknowledge and avoid these seven common scale-up hazards:

1. Leaving Research Behind

When significant cash is needed pre-launch for investments in pivotal trials and building out the manufacturing and commercial functions, research is often an area that feels investment-constrained. Companies must walk the fine line between going "all hands on deck" for their first launch and ensuring that the discovery engine has sufficient resources to continue to fill the pipeline. While there are no easy solutions, management should ensure that a systematic portfolio prioritization and stage-gate framework are in place to make investment trade-offs that ensure research investments are considered through the lens of long-term corporate growth as well as near-term cash requirements.

> *"As a biopharma scales up, new functions are typically established by hiring VP or other executive-level individuals who then go on to build out those functions."*

2. Missing Commercial And Medical Input On Pivotal Trial Design

Emerging biopharmas typically establish the core commercial and medical functions *after* pivotal trials are already underway. By waiting this long, companies risk missing out on informing clinical development plans with a robust market understanding, including who their key customers are, what trial endpoints and comparators are most meaningful to drive adoption, and how US and ex-US pricing and market access negotiations can be best supported by trial evidence. Management should consider onboarding a handful of core marketing, market access and medical affairs team members *prior* to designing pivotal trials to ensure that such findings and feedback can be incorporated into the pivotal trial design.

3. Delaying Clinical And Commercial Manufacturing Scale Up

Establishing a validated supply chain for GMP-grade drug products and drug substances is a necessary condition for late-stage clinical trials and filing, and doing so can take years. This is becoming increasingly critical as biopharmas launch novel therapeutic modalities. For example, viral vector manufacturers have been identified as a bottleneck for gene therapy commercialization, requiring several years' lead time for process development and scale-up. While not all such challenges can be foreseen, management should ensure that manufacturing timelines are developed sufficiently in advance and incorporated into clinical development, filing and launch plans.

4. Underinvesting In Back Office Functions

While companies know they need to build clinical, medical and commercial functions prior to launch, back office functions such as HR, IT, legal and finance are commonly overlooked. Delaying their build-out can result in process inefficiencies that can compound to threaten the launch if not addressed quickly. For example, recruiting and onboarding of talent can slow down critically without sufficient HR resources.

Exhibit 2 shows how the HR function typically *should* scale up to meet the needs of the growing organization. Another example is that enterprise-wide software decisions cannot be made efficiently without a sufficiently staffed IT department.

5. Neglecting Program Management

Strong program management is critically important to drive cross-functional collaboration and streamline tasks by development program to limit functions operating in silos. While project managers often exist in R&D, as assets advance through clinical development and show commercial potential, it is important for a company-wide program management function to be formed to facilitate cross-functional alignment and manage the interface between executive leadership and each program team.

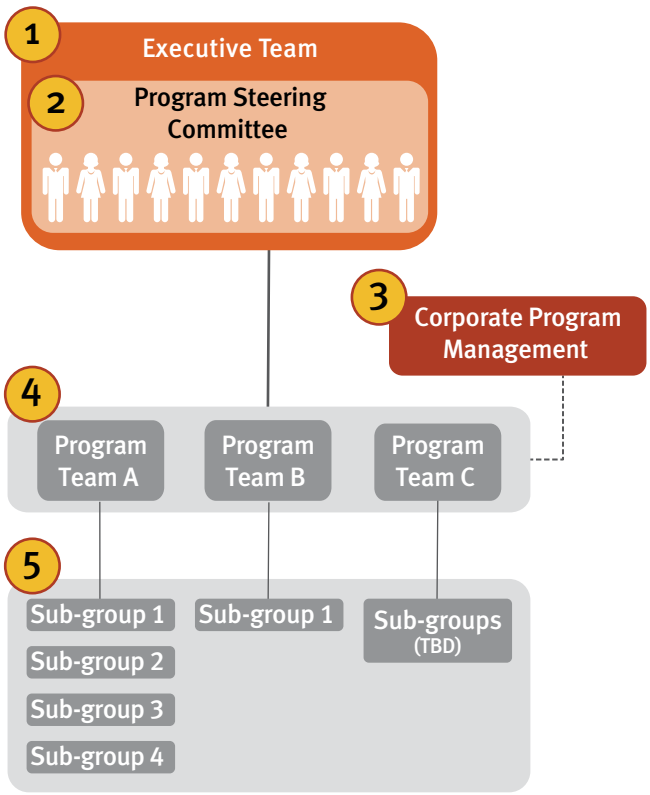
Our perspective is that program management should report to a corporate Executive Leadership Team (ELT) member, potentially the CEO, to ensure that the function is perceived as objective and empowered by leadership. Without such empowerment, functional leaders may not take program managers seriously, preventing them from effecting change and holding individuals accountable. Effective program management requires senior leadership to buy into its importance and emphasize it as such in company-wide communications. Exhibit 3 presents an example of a governance structure with corporate program management liaising between individual program teams and executive leadership.

6. Unclear Governance And Reporting Structures

As a biopharma scales up, new functions are typically established by hiring VP or other executive-level individuals who

Exhibit 3

Example Of Governance Structure With Centrally Reporting Program Management



1 **Executive Leadership Team (ELT):** Focused on corporate strategy, setting priorities and monitoring cross-functional execution

2 **Program Steering Committee:** Subset of ELT members focused on providing guidance to program teams, regulatory strategy, clinical trial design, etc.

3 **Corporate Program Management:** Serve as facilitator between Steering Committee and Program teams, and gaining alignment with functional heads

4 **Program Teams:** Oversee program execution and provide platform for alignment on issues not requiring functional head input, clinical protocol review, trial product supply, etc.

5 **Program Team Sub-groups:** Plan and execute activities relevant to subset of functions, NDA development, packaging, etc.; escalate issues when required

Exhibit 4
Organizational Scale Up Self-Assessment

	SCALE UP STATUS QUESTION	ALL-SET	OK	WORK-TO-DO
1	Have the go-to-market strategy and customer-facing model been clearly defined and socialized with the ELT and board?			
2	Do we have a process to systematically make investment trade-offs that ensure long-term growth?			
3	Are the pivotal trials designed to support pricing and reimbursement, not just approval?			
4	Are commercial-scale manufacturing timelines established and on track?			
5	Does our scaleup plan explicitly incorporate back-office needs (HR, IT, Legal and Finance) to support the rest of the company?			
6	Does our Program Management function drive programs forward with cross-functional input, on time and on budget?			
7	Are our governance structure and processes well-understood throughout the organization?			
8	Are we on track with hiring of critical talent?			

SOURCES FOR ALL EXHIBITS: L.E.K. analysis

then go on to build out those functions. This growth in management means that a relatively flat reporting structure — which may have worked for the executive leadership team (ELT) when the organization had 30 to 60 full-time equivalents (FTEs) — may not be as effective as headcounts quadruple or more over two to three years when initiating pivotal trials and preparing to launch. To minimize costly overlaps and gaps, the ELT needs to review and evolve organizational responsibilities, reporting hierarchies and governance structures as the company reaches growth inflection points.

7. Insufficient Time To Hire Key Talent

Companies are often behind their hiring timelines because finding the right talent in competitive markets usually takes much longer than expected. In particular, companies preparing to launch their first product may not be well-known or could be seen as less attractive to high-quality yet risk-averse candidates. Management would be wise to build in sufficient buffer time and start recruiting for required positions at least three to six months in advance, and even more for executive roles like chief commercial officer or specialized roles in such areas as quality, regulatory, biostatistics and pharmacovigilance.

Keeping Track: Pointers For Self-Assessment

We close with a few questions based on these scale-up hazards that senior leadership can use to self-assess whether their organizations are on track (*see Exhibit 4*). While there are many key questions for management to consider, it is our experience that failure to address these seven potential hazards creates significant obstacles to a successful launch on time and on budget. Preparing to commercialize the first product is one of the most challenging moments in a biopharma company's evolution, but having executive leadership committed to the launch, well-informed about potential roadblocks and possessing the right tools to address the issues is foundational to preparing the organization for success.

IV124241

About the authors: Pierre Jacquet is a managing director and global head of L.E.K. Consulting's life sciences practice. Peter Rosenorn is also a managing director in the life sciences practice. And Aditya Natarajan is a consultant in the same group.

Immuno-Oncology: Halfway To Adulthood

Almost a decade on since the first approval for an immuno-oncology therapy, *In Vivo* analyzes the current landscape, the evolution of combination cancer treatments that use the immune system to target disease and future commercial potential for the market.

BY DANIEL CHANCELLOR

April 29, 2019, marks immuno-oncology's (IO) ninth birthday, following the approval of *Provenge*, the first drug that harnesses the body's immune system to fight cancer, in April 2010. Since this landmark event, it has been a tremendous decade for the field, with IO becoming part of the standard-of-care in a range of treatment settings and the Nobel Prize being awarded for the discovery of immune checkpoint inhibition.

It is the checkpoint inhibitor drug classes that are leading the IO revolution and will act as a foundation for the next decade of oncology research. *In Vivo* has reviewed the childhood years of IO and made some predictions of what the future holds as it reaches double digits and matures through adolescence.

An Explosion In Trial Activity

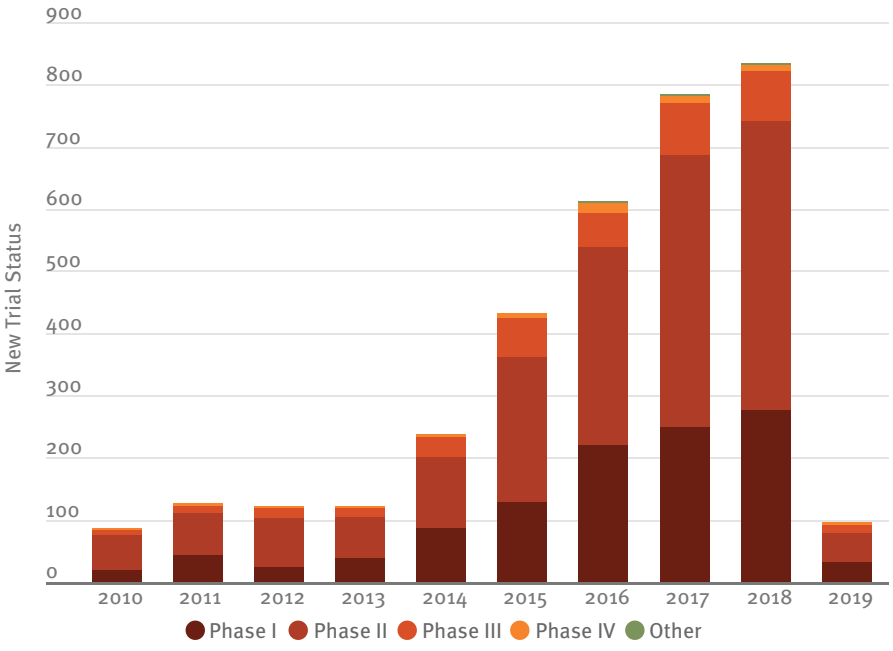
With clinical trials being the main driving force for the biopharmaceutical industry, reviewing trends provides both an interesting snapshot of past successes and a glimpse into what the future might hold. In total, Informa Pharma Intelligence's Trialtrove database lists 3,450 industry-sponsored clinical trials from January 2010, incorporating drugs with an IO mechanism for an oncology indication. The top-line analyses show that trial activity is booming, in particular due to the proliferation of combination studies and the application of IO to an increasing number of tumor types.

At the start of the decade, IO was still very much experimental and just 86 such trials were initiated in 2010. However, this has increased tenfold, with a record 833 clinical trials initiated by industry last year; more than two every single day. In particular, the approvals of the first PD-1 checkpoint inhibitors in 2014 coincided with a period of intense acceleration, as competitors reacted to the potential showed by *Opdivo* (nivolumab; **Bristol-Myers Squibb Co.**) and *Keytruda* (pembrolizumab; **Merck & Co.**). Even through the latter part of this decade, there has been considerable activity with early-stage, Phase I research, suggesting that IO is a long way from reaching maturity and there are many new clinical hypotheses to test (*see Exhibit 1*).

Across this dataset, over 50 discrete cancers have been investigated. The majority of development has occurred in the prevalent solid tumors, although non-Hodgkin's lymphoma appeared prominently at the start of the decade. This was the main indication for development of anti-CD20 antibodies, a target expressed on immune cells, but is not an IO approach in the truest sense. As the decade progressed, melanoma notably gained prominence as the first indication with proof-of-concept for checkpoint inhibition to be established. Success in this hard-to-treat disease, and the rise of PD-1 inhibitors, enabled drug developers to pivot towards the hugely important non-small cell lung cancer (NSCLC) indication, which is the single most studied indication through the last decade. There has also been a consistent rise in trials investigating tumors classified by a molecular or genetic signature, rather than

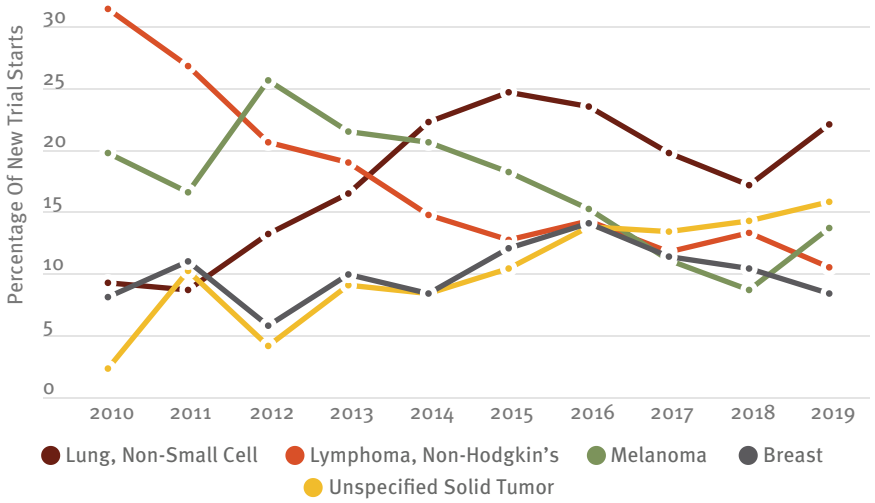
Exhibit 1

Number Of IO Trials Has Rocketed Since 2014



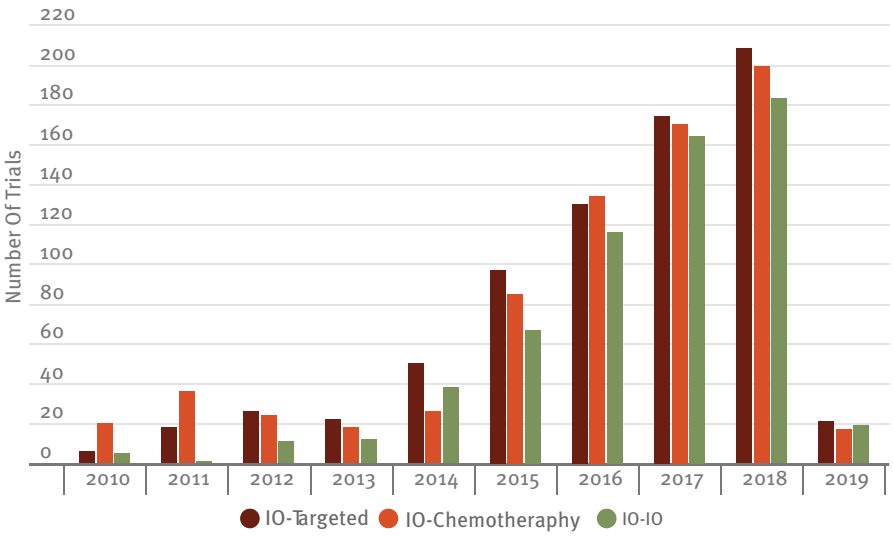
SOURCE: Trialtrove

Exhibit 2
NSCLC Trials Have Increased Over The Last Decade



SOURCE: Trialtrove

Exhibit 3
The Number Of IO-IO Combination Trials Is On The Rise



SOURCE: Trialtrove

by their location (*see Exhibit 2*).

As IO is being trialed across the entire spectrum of oncology, developers have made a concerted shift towards establishing IO in new populations, especially earlier in the treatment algorithm. Part of this strategy has involved combining IO with the existing standard of care. The rationale behind combining IO with another treatment approach, typically chemotherapy, targeted therapy, or another IO drug, is to treat patients that may not respond to monotherapy, or to provide a deeper and more durable response than that achieved by a single agent. Since 2015, the majority of new trials have involved a combination regimen, and it is feasible that almost all IO trials in the future will involve multiple agents.

Each of the three common combination treatment modalities are being explored extensively. There are marginally more trials of IO in conjunction with a targeted treatment, although the IO-IO combination is increasing at the fastest rate as developers seek to discover new targets to combine with a PD-1 inhibitor backbone. The most popular mechanism in this setting is IDO inhibition, which has met with multiple failures so far, shifting attention towards a plethora of new targets such as LAG3, 4-1BB and OX40 (*see Exhibit 3*).

A Lucrative Market That's Still Growing

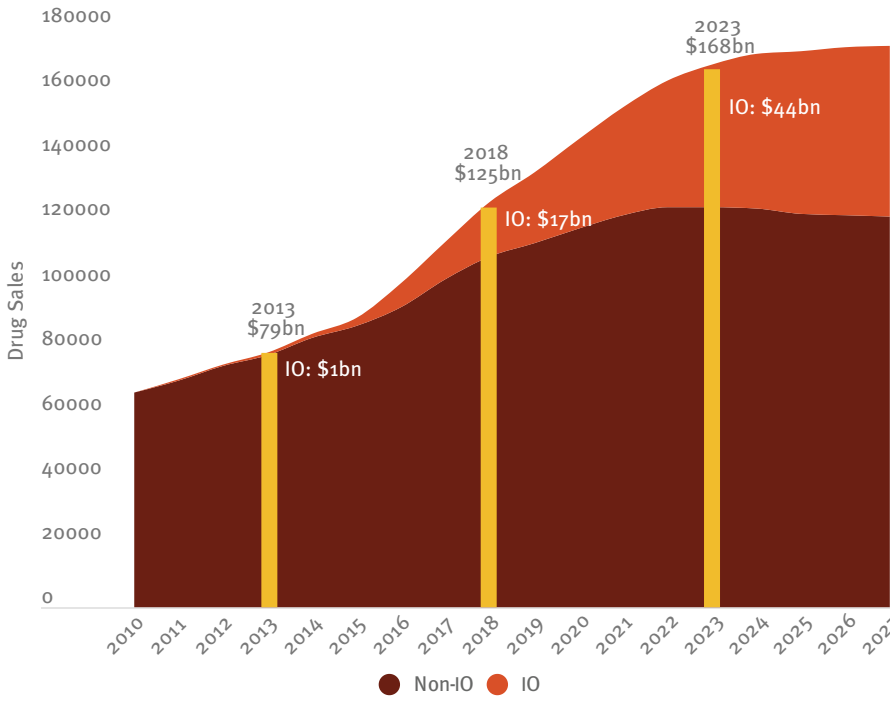
The huge growth in clinical trial activity is very much a proxy for the market direction. As IO has transitioned from experimental to foundational, with ever-growing product labels for some of the leading PD-1 inhibitors, the commercial landscape has become increasingly lucrative. In total, Datamonitor Healthcare estimates that the oncology market was worth $125bn globally in 2018. This has grown by 50% in the last five years, and almost doubled since the start of the decade. Conventional oncology drugs have been behind much of this growth, in addition to macro factors such as patient demographics, improved survival statistics and drug price inflation.

New IO drug classes are also making an important contribution to the wider oncology market, with sales of around $17bn in 2018. It is these drugs that will be fundamental to the continued growth of oncology, with even conservative forecasts placing their potential at $44bn by 2023, by which time IO will account for around one quarter of the total oncology market. Much of this growth will belong to the PD-1 inhibitor class, with all six currently approved PD-1s expected to become blockbusters. This follows their continued approvals in new tumor types and treatment settings, as well as widespread acceptance among treatment guidelines, payers and physicians. Exhibit 4 shows how sales of conventional oncology drugs will begin to plateau, leaving IO as the all-important growth driver.

Payers And Market Access Will Ultimately Constrain IO Market

Various estimates place the cost of treating cancer at up to 10% of total health care spending in major markets, and as *Exhibit 4* shows, the direct costs associated with pharmaceuticals have risen greatly in recent years. When you combine this with pressure on payers to provide access to hugely important checkpoint inhibitors, which can cost

Exhibit 4
IO Will Significantly Contribute To Growth Of The Oncology Market



SOURCE: Datamonitor Healthcare

$150k per patient, it is clear that the growth of IO is only sustainable up until a point. In order to fund continued access to all of the cancer patients that may benefit, either oncology budgets must mirror this dramatic growth, or other areas of health care spending must be targeted for savings. A German payer told *In Vivo*: "We see around a 15% budget impact increase in oncology from last year to this year, and 15% every year. We will see 30% or 40% if those combinations, all of them, come to the market."

Greater competition among the PD-1 class should breed greater competition in pricing, and an overall improvement in affordability. At the moment, many treatment settings only have one or two approved IO options, although this will change as some of the later entrants achieve broader product labels. At this time, the balance of power will certainly shift towards payers, who will be in a strong negotiating position to secure discounting to win reimbursement. "There has not been any steep discounting yet, but as there is more and more competition, in order for them to entice physicians to use their product, they probably will discount through the distribution chain, and the average sales price will decline," a US-based payer said.

Combination IO will also be emerging into mainstream clinical practice over the next few years, which brings a potential doubling in direct treatment costs. In the longer-term, indication-specific pricing is a viable solution, whereby a single drug has multiple price points, depending on the diagnosis and treatment strategy. This adds a great deal of complexity and the necessary laws and systems are not yet in place to facilitate this on a large scale. In the meantime, there is relatively little that can be done to control spending with combinations, except for cases when a single manufacturer owns all of the constituents and can effectively discount one of the drugs, for example Bristol-Myers Squibb marketing both Opdivo and *Yervoy* (ipilimumab) for melanoma. A European payer said: "It is easier to use it if the combination comes from the same manufacturer. If it comes from different companies, it is not always clear whether a drug was used as a single agent or in combination, and the manufacturer is not willing to pay a hidden rebate in a price-volume agreement for its monotherapy setting."

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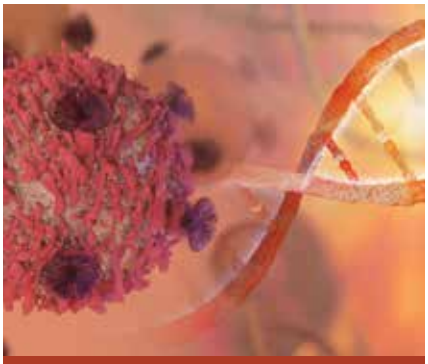

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On the Move

Recent executive appointments in the life sciences industry

CHRIS FANG

KELD FLINTHOLM JORGENSEN

DIDIER LE NORMAND

ANTONY LOEBEL

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Victoria Smith	Amphivena Therapeutics Inc	Chief Scientific Officer	Gilead Sciences	Leader, Biologics and Target Biology Group	5-Mar-19
Joachim Fruebis	BlueRock Therapeutics	Chief Development Officer	Bioverativ	Senior Vice President, Clinical Development	18-Mar-19
Adam Crystal	C4 Therapeutics	Chief Medical Officer	Novartis Institutes for BioMedical Research	Lead, Development Programs	13-Mar-19
Jean Casner	Cantel Medical Corp	Chief Human Resources Officer and Senior Vice President	Merck	Lead, Human Resources	18-Mar-19
Thomas Moffatt	Cardiol Therapeutics Inc	Chief Commercial Officer	Rx Drug Mart Inc	Chief Operating Officer and Vice President, Operations	6-Mar-19
Mira Rosenzweig	Check-Cap	Chief Financial Officer	Entera Bio Ltd	Chief Financial Officer	28-Apr-19
Gary Titus	Cytori Therapeutics Inc	Chief Financial Officer	UroGen Pharma Ltd	Chief Financial Officer	1-Apr-19
Athanasios Papadopoulos	Emergex Vaccines Ltd	Chief Medical Officer	Sanofi	Vice President, Senior Director	1-Mar-19
Lyndal York	Fisher & Paykel Healthcare Ltd	Chief Financial Officer	Asaleo Care	Chief Financial Officer	1-Mar-19
Keld Flintholm Jorgensen	H. Lundbeck AS	Executive Vice President, Chief Business Officer	Roche	Head, Strategic Partnering	4-Apr-19
Chris Fang	Humacyte	Chief Medical Officer	Amaris Health	Managing Partner	6-Mar-19

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THOMAS MOFFATT

ANTHANASIOS PAPADOPOULOS

JOHN SHERIDAN

PRIYA SINGHAL

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Jacqueline E. Shea	Inovio Pharmaceuticals Inc	Chief Operating Officer and Executive Vice President	Aeras	Chief Executive Officer and Chief Operating Officer	12-Mar-19
Troy Ignelzi	Karuna Pharmaceuticals	Chief Financial Officer	scPharmaceuticals	Chief Financial Officer	5-Mar-19
Trui Hebbelinck	LivaNova PLC	Chief Human Resources Officer	Shell	Vice President, Human Resources Trading and Supply	18-Mar-19
Bryan Reasons	Mallinckrodt plc	Chief Financial Officer	Impax Laboratories	Senior Vice President and Chief Financial Officer	18-Mar-19
Didier Le Normand	Minoryx Therapeutics SL	Group Chief Financial Officer and General Manager, Belgium	STAT-Dx Life SL	Chief Financial Officer, Finance and Operations	12-Mar-19
Sharon Klugewicz	Misonix Inc	Chief Operating Officer	Chembio Diagnostics Systems	Chief Quality and Regulatory Affairs Officer	4-Mar-19
D. Keith Grossman	Nevro Corp	Chief Executive Officer, President and Director	Thoratec Corp	President, Chief Executive Officer and Director	19-Mar-19
Hsiao D. Lieu	NGM Biopharmaceuticals Inc	Chief Medical Officer and Senior Vice President	Genentech	Vice President, Early Clinical Development	20-Mar-19
Ran Zheng	Orchard Therapeutics	Chief Technical Officer	Amgen	Vice President, Development Supply Chain	18-Mar-19
John Temperato	RDD Pharma Ltd	Chief Executive Officer	Atlantic Healthcare plc	President, US and Chief Operating Officer	20-Mar-19

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Francine R. Kaufman	Senseonics	Chief Medical Officer	Medtronic Diabetes	Chief Medical Officer and Vice President, Global Clinical, Regulatory and Medical Affairs	6-Mar-19
Andrew Pucher	Tilray	Chief Corporate Development Officer	Goldman Sachs	Managing Director	13-Mar-19
Priya Singhal	Zafgen	Head, Research and Development	Biogen	Senior Vice President, Global Head, Safety and Benefit Risk Management	4-Mar-19

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
Philipp Maerz	Allergopharma GmbH & Co KG	Chief Executive Officer	Chief Operating Officer	1-Mar-19
Deborah Rathjen	Bioasis Technologies Inc	Executive Chairman, Chief Executive Officer and President	Executive Chairman	11-Mar-19
George L. Fotiades	Cantel Medical Corp	Chief Executive Officer, President and Director	Vice Chairman, Chairman of Nominating Committee and Member of Audit Committee	5-Mar-19
Junichi Koga	Daiichi Sankyo Co Ltd	Senior Executive Officer, Global Head, Research and Development	Senior Executive Officer, Head, Research and Development	1-Apr-19
Peter Manley	Genetic Signatures	Chief Financial Officer and Company Secretary	Chief Financial Officer	4-Mar-19
Dirk De Naeyer	Kiadis Pharma	Chief Operations Officer	Head, Supply Chain	5-Mar-19
Jon Wells	Midmark Corp	Chief Commercial Officer	Vice President, Marketing	4-Mar-19
Alex DePaoli	NGM Biopharmaceuticals Inc	Chief Translational Officer and Senior Vice President	Chief Medical Officer and Vice President	20-Mar-19
Pius S. Hornstein	Sanofi	General Manager, China, and China Emerging Markets Global Busniess Unit	General Manager, Brazil	1-Mar-19
Patricia Altavilla	Suneva Medical Inc	Chief Executive Officer	Chief Operating Officer	6-Mar-19
Antony Loebel	Sunovion Pharmaceuticals Inc	Chief Executive Officer and President	Executive Vice President, Chief Medical Officer and Head, Global Clinical Development	1-Apr-19
John Sheridan	Tandem Diabetes Care Inc	Chief Executive Officer and President	Chief Operating Officer and Executive Vice President	1-Mar-19
Jonathan Eckard	Tyme Technologies Inc	Chief Business Officer	Chief Scientific Affairs Officer	15-Mar-19
Michele Korfin	Tyme Technologies Inc	Chief Operating Officer	Chief Commercial Officer	15-Mar-19

DIRECTORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Christine Yingli	Ansell Ltd	Non-Executive Director	1-Apr-19
Karen Smith	Antares Pharma	Director	4-Mar-19
Geoffrey A. Block	Ardelyx Inc	Director	14-Mar-19
Pierre Legault	Bicycle Therapeutics Ltd	Chairman	18-Mar-19
Michal Votruba	BioXcel Therapeutics Inc	Director and Member, Audit Committee	11-Mar-19
Rebecca Taub	BriaCell Therapeutics Corp	Director	18-Mar-19
Vaughn C. Embro-Pantalony	BriaCell Therapeutics Corp	Director	18-Mar-19
Peter B. Luther	CeQur SA	Director	18-Mar-19
Seamus Mulligan	Emergent BioSolutions Inc	Director	19-Mar-19
Kathleen Sebelius	Exact Sciences Corp	Class II Director and Member, Corporate Governance and Nominating Committee and the Innovation, Technology and Pipeline Committee	4-Mar-19
Kit Wei Lui	InvitroCue Pte Ltd	Director	11-Mar-19
Hubert Birner	leon-nanodrugs GmbH	Chairman, Supervisory Board	1-Mar-19
Andrea J. Goldsmith	Medtronic plc	Independent Director	11-Mar-19
Elizabeth (Bess) Weatherman	Nevro Corp	Independent Director	19-Mar-19
Kevin O'Boyle	Nevro Corp	Independent Director	19-Mar-19
Senator Orrin G. Hatch	Predictive Technology Group Inc	Director	19-Mar-19
Lara S. Sullivan	Rexahn Pharmaceuticals Inc	Director, Chair, Business Devlopment Committee and Member, Nominating and Corporate Governance Committee	1-Mar-19
Jeffrey C. Lightcap	RTI Surgical Inc	Director	8-Mar-19
Cynthia Smith	Spero Therapeutics	Director	19-Mar-19

ADVISORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
M. Patricia Rivera	bioAffinity Technologies Inc	Chairman, Scientific and Medical Advisory Board	12-Mar-19
Gordon H. Williams	Cereno Scientific AB	Scientific Advisory Board Member	11-Mar-19
Lakhmir Chawla	ExThera Medical Corp	Chairman, Scientific Advisory Board	11-Mar-19
Stefanie Johns	Hoth Therapeutics Inc	Scientific Advisory Board Member	19-Mar-19
Helene Arditti	Innate Pharma SA	Strategic Executive Advisor	12-Mar-19
Martin Tallman	Moleculin Biotech Inc	Scientific Advisory Board Member	18-Mar-19
Joshua Dunaief	Mperia Therapeutics Inc	Clinical Advisory Board Member	18-Mar-19
John Singerling, III	Nephron Pharmaceuticals Corp	Senior Advisory Board Member	12-Mar-19
Timothy M. Wright	Regulus Therapeutics	Scientific Advisor	15-Mar-19

Deal-Making

Covering deals made March 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.

Strategic Transactions is updated daily with in-depth deal analysis, structural and financial terms, and links to SEC-filed contracts.

For information about access please contact Customer Care at 888-670-8900 or PharmaNewsSales@informa.com

IN VITRO DIAGNOSTICS

Alliances

Natera to launch *Signatera* test in China on **BGI**'s *DNBseq* NGS platform

A. Menarini gets license to **Curetis**' *Unyvero* platform

Financings

Epizyme nets $160.4mm through concurrent offerings of common and preferred shares

Exact Sciences nets $634mm through upsized public notes offering

Invitae nets $184.9mm in FOPO

NanoString nets $54mm through public offering

MEDICAL DEVICES

Mergers & Acquisitions

Alcon acquires IOL company **PowerVision** for $285mm, plus potential earn-outs

Smith & Nephew acquires **Brainlab**'s orthopedic joint reconstruction business

Smith & Nephew buys **Osiris Therapeutics** in deal valued at $660mm

Stryker pays $110mm for **OrthoSpace**

Alliances

MyungMoon Bio to sell **ACell**'s wound matrix products in South Korea

Shionogi licenses **Akili**'s digital medicine candidates for ADHD, ASD

Edwards invests $35mm in **Corvia**; gets option to buy

Micro Interventional Devices, **Oscor** team up in structural heart disease

Financings

Apollo Endosurgery enters loan agreement with Solar Capital

PIPE brings in $10mm for **ShockWave** concurrent with IPO

ShockWave nets $90.1 via IPO

Titan Medical nets $26.7mm via public offering

PHARMACEUTICALS

Mergers & Acquisitions

Biogen pays $877mm in cash for **Nightstar**

Oncternal reverse merges with **GTx**

Sorrento's **Scilex** enters up to $347mm merger agreement with **Semnur**

Alliances

Alexion gains another anti-FcRn molecule through deal with **Affibody**

Zealand Pharma and **Alexion** work on treatments for complement-mediated diseases

Ambrx and **BeiGene** pen biologics development and licensing agreement

Lilly pays $40mm up front in new immunology deal with **ImmuNext**

Laboratoires Thea gets certain rights to **OliX**'s preclinical AMD candidate

LG Chem Life Sciences licenses lung cancer vaccine candidate from **PDC*line**

Nicox grants **Ocumension** certain Asian rights to *Zerviate*

Nippon Shinyaku gains exclusive Japanese rights to **Zogenix**'s *Fintepla*

Secura Bio gains worldwide license to **Novartis**'s *Farydak* multiple myeloma drug

Servier options worldwide rights to **Oncodesign**'s LRRK2 kinase inhibitors in PD

Petra Pharma enters licensing agreement with **Takeda**

Pfizer, **Vivet** team up in Wilson disease; Pfizer gets 15% equity stake with future option to acquire

Takeda enters $710mm gene therapy partnership with **StrideBio**

Financings

Aldeyra enters into term loan facility with Hercules Capital

Evolus enters $100mm loan agreement with Oxford Finance; initially draws down $75mm

Apellis nets $110mm through public offering

Aptevo nets $20mm through public offering

Ascendis nets $470mm via FOPO of ADSs

Bio-Path Holdings nets $17.2mm through registered direct offering

Biohaven completes $125mm private placement through Royalty Pharma; could get $75mm more

Biohaven buys **GW Pharmaceuticals**' PRV for $105mm

Public offering nets $16.3mm for **Cellular Biomedicine**

Curis sells some *Erivedge* royalties to Oberland Capital

Public offering nets $108mm for **CymaBay**

Dermira nets $122.2mm in FOPO

Genfit completes initial public offering of ADSs in US; nets $116.2mm

Genfit nets $9.4mm in PIPE concurrent with US IPO

Horizon Pharma nets $328mm in public offering

IMV nets $Cdn29mm through public offering

Infinity enters royalty monetization agreement with HealthCare Royalty Partners

Ligand monetizes *Promacta* royalties through $827mm transaction with Royalty Pharma

Matinas BioPharma nets $28.2mm through public offering

Public offering nets $92mm for **Mersana**

FOPO nets $236.1mm for **MyoKardia**

Follow-on nets $11.6mm for **Oragenics**

Portola enters $125mm loan agreement with HCR, Athyrium; gets $62.5mm at closing

Precision BioSciences files for IPO

FOPO nets $47mm for **resTORbio**

Sarepta nets $365.7mm via latest public offering

Public offering nets $24.1mm for **TG Therapeutics**

IN VITRO DIAGNOSTICS

ALLIANCES

BGI GENOMICS CO. LTD.
NATERA INC.

BGI Genomics Co. Ltd. will commercialize in China **Natera Inc.**'s *Signatera* minimal residual disease (MRD) and molecular monitoring test. The companies will also partner on the development of reproductive health tests in certain territories. (Mar.)

BGI will provide $50m in up-front licensing fees, prepaid royalties, and future milestone payments, in addition to ongoing royalty payments. Natera will prepay BGI $6m for sequencing services associated with the agreement. For research-use only (not yet in diagnostic procedures) to assess MRD and monitor treatment, Natera's *Signatera*, is individualized to a specific patient to identify 16 unique, clonal, somatic variants, followed by multiplex PCR and ultra-deep sequencing. The ctDNA assay has demonstrated potential across several tumor types, including lung, colorectal, bladder, and breast. Although mainly focused on molecular diagnostics within reproductive health, Natera recently expanded indications into renal transplant rejection and oncology. Under the ten-year agreement, BGI will offer Natera's *Signatera* test in China, first through specialty hospital networks and then more broadly once Chinese regulatory approval for use of the *Signatera* test on the *DNBseq* platform is achieved. The partners will also co-develop reproductive health tests in select markets on BGI's sequencing instruments, including the *DNBseq* next-generation sequencing (NGS) platform. BGI's *DNBseq* NGS technology supports its portfolio of cell-free DNA genetic testing for reproductive health, including carrier screening, newborn screening for rare disease, and preimplantation genetic screening (PGS).

MENARINI GROUP
A. Menarini Diagnostics SRL
CURETIS NV

In a long- term agreement, **Curetis NV** granted **A. Menarini Diagnostics SRL** exclusive rights to market and distribute its *Unyvero* platform and cartridges in eleven European countries. (Mar.)

The partnership initially covers distribution in Germany, France, Belgium, the Netherlands, Luxembourg, the UK, Switzerland, Italy, Spain, Portugal, and Sweden. Curetis and Menarini may extend the licensing to include additional international territories in the future. The *Unyvero A50* molecular diagnostics platform uses multiplex PCR technology to simultaneously and rapidly detect a wide variety of microorganisms, antibiotic resistance markers, or toxins from one sample using a disposable cartridge. Menarini will sell the platform as well as all CE-marked cartridges. Curetis will transfer to Menarini all active commercial customer accounts and potential future customer accounts. The parties have also entered a 90-day period of exclusive negotiations for a license to Curetis *Unyvero A30 RQ* in the field of oncology in certain territories including Europe, the Middle East, and Africa. That product is currently in development.

FINANCINGS

EPIZYME INC.

Epigenetics firm **Epizyme Inc.** netted $160.4m through concurrent public offerings. The company sold 11.5m common shares (including the overallotment) at $11.50 for net proceeds of $123m, and also sold 350,000 Series A preferred shares (including the overallotment) at $115 for net proceeds of $37.4m. Funds will support ongoing development, regulatory activities, and future commercialization of tazemetostat for epithelioid sarcoma and follicular lymphoma; R&D of other projects, including EZM8266 for sickle cell disease; and working capital. (Mar.)

Investment Banks/Advisors: Citigroup Inc.; Cowen & Co. LLC; HC Wainwright & Co.; Jefferies & Co. Inc.; Wedbush PacGrow Life Sciences

EXACT SCIENCES CORP.

Exact Sciences Corp. (molecular diagnostics for early cancer detection) netted $634m through a public offering of $650m principal amount of 0.375% senior notes due 2027. (The offering was upsized from $600m.) The notes convert to common at a rate of 8.9554 shares per $1k principal amount, or $111.6645 per share. The company's stock averaged $89.76 at the time of the sale. (Mar.)

Investment Banks/Advisors: BTIG LLC; Bank of America Merrill Lynch; Canaccord Genuity Inc.; Cowen & Co. LLC; Craig-Hallum Inc.; Robert W. Baird & Co. Inc.; William Blair & Co.

INVITAE CORP.

Genetic testing firm **Invitae Corp.** netted $184.9m via a follow-on public offering of 10.35m common shares (including full exercise of the overallotment) at $19 each. (Mar.)

Investment Banks/Advisors: Cowen & Co. LLC; JP Morgan & Co.; SVB Financial Group

NANOSTRING TECHNOLOGIES INC.

NanoString Technologies Inc. (molecular diagnostics and translational research) netted $54m through the public sale of 2.5 million common shares at $23. Selling stockholders also sold 2 million shares in the offering. (Mar.)

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

MEDICAL DEVICES

MERGERS & ACQUISITIONS

NOVARTIS AG
Alcon Inc.
POWERVISION INC.

Novartis AG's eye care division **Alcon Inc.** agreed to acquire private intraocular lens (IOL) implant maker **PowerVision Inc.** (Mar.)

Alcon will pay $285m up front and could additionally provide earn-outs starting in 2023 based on the achievement of regulatory and commercial milestones. Founded in 2002, PowerVision is developing an accommodating fluid-based IOL technology to correct cataracts and also restore both near and intermediate vision and distance vision. Different from the multifocal approach of most presbyopia-correcting IOLs (that often restore just distance vision), PowerVision's design instead transports fluid within the implanted IOL to create a continuously variable monofocal lens, using the eye muscles' natural accommodating contraction response. This technology, not yet commercially available, is expected to allow cataract surgery or presbyopic patients to actively focus on objects and provide a continuous range of vision that could eliminate the need for bi-focals for near and far vision. Gaining PowerVision's technology will help Alcon further boost its existing ophthalmic surgery offerings, which already include the *AcrySof IQ* monofocal IOLs for cataracts; the *CyPass* minimally invasive micro-stent for glaucoma (gained through its 2016 acquisition of **Transcend Medical**); and the *iLux* device for dry eye (acquired in its December 2018 buy of **Tear Film Innovations**). As announced in mid-2018, Novartis is in the process of spinning off the device-focused parts of Alcon into a separate independent company expected to be completed in 1H 2019.

SMITH & NEPHEW PLC
BRAINLAB AG

On the same day it paid about $660m for **Osiris**, **Smith & Nephew PLC** is now acquiring **Brainlab AG**'s orthopedic joint reconstruction business for an undisclosed sum. (Mar.)

S&N recently issued a statement saying that it will focus on making investments that establish its presence in multi-asset digital surgery and robotics. This transaction is the first step in attaining that goal. The acquired Brainlab business offers digital workflow tools--cloud computing, tracking, augmented reality, robotics, artificial intelligence, machine learning, image fusion, and anatomical segmentation--for surgical procedures that can aid in pre-operative planning, navigation during surgery, and post-op evaluation. These offerings can greatly improve patient outcomes. In addition to the products, S&N also gains Brainlab's orthopedic salesforce and will combine the business into its own robotics commercial organization. Both firms will team up to create applications for use in sports medicine and orthopedic reconstruction and could eventually move into other surgical areas.

SMITH & NEPHEW PLC
OSIRIS THERAPEUTICS INC.

Expanding its wound healing and tissue repair portfolio, **Smith & Nephew PLC** is paying $19 per share in cash (a 7% premium based on the 10-day market average) to acquire regenerative medicines firm **Osiris Therapeutics Inc.** The equity value of the deal is approximately $660.5m. (Mar.)

S&N will finance the transaction with a combination of cash and debt. The company was particularly attracted to Osiris' key revenue-generators *Grafix* and *Stravix* cryopreserved skin substitutes. *Grafix* is a placental membrane that can be applied directly to wounds, including those with exposed bone and tendon. Just five months ago, Osiris launched *GrafixPL PRIME*, a lyopreserved placental amniotic membrane that is stored at room temperature. *Stravix* is a cryopreserved human placental tissue containing umbilical amnion and Wharton's jelly for surgical applications. *Stravix* is manufactured using a process that retains the natural components of fresh placental tissue and can be used as a surgical covering or wrap for several procedures such as tendon repair, bunionectomies, and fibromatosis. Osiris also offers the viable bone matrix *BIO4* (sold by **Stryker** under a December 2014 deal) and the *Cartiform* osteochondral allograft for articular cartilage repair (distributed by **Arthrex** via an October 2014 tie-up). Investment Banks/Advisors: Cantor Fitzgerald & Co. (Osiris Therapeutics Inc.)

STRYKER CORP.
ORTHOSPACE LTD.

Stryker Corp. is paying $110m up front in cash to acquire closely held Israeli device firm **OrthoSpace Ltd.** Strkyer could shell out another $110m in earn-outs. (Mar.)

Ten-year-old OrthoSpace developed the *InSpace* sub-acromial spacer for treating massive irreparable rotator cuff tears. The product is based on a biodegradable balloon system that is implanted via a minimally invasive procedure and is designed to alleviate pain and shorten the rehabilitation period. The balloon creates a space between the two bones whose friction causes the most pain. After the spacer is in place, there's no friction between the bones. *InSpace* is available in 30 countries worldwide however it is still in clinical studies in the US.

ALLIANCES

ACELL INC.
MYUNGMOON BIO CO. LTD.

ACell Inc. granted **MyungMoon Bio Co. Ltd.** exclusive rights to market and distribute its wound management matrix products in South Korea. (Mar.)

Included in the deal are the *Cytal* and *MicroMatrix* products, which are comprised of naturally-occurring (porcine derived) urinary bladder matrix (UBM). Both facilitate the remodeling of functional tissue and are indicated for a variety of 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. MicroMatrix is supplied in particle form (for application directly to the wound bed or as a paste when combined with sterile saline) while *Cytal* is available in one-, two-, three-, and six-layer sheets. (The two can be used together, with application of *MicroMatrix* preceding application of *Cytal*.)

AKILI INTERACTIVE LABS INC.
SHIONOGI & CO. LTD.

Shionogi & Co. Ltd. secured exclusive development, marketing, and commercialization rights in Japan and Taiwan to **Akili Interactive Labs Inc.**'s digital therapeutic candidates AKLT01 (under review by the FDA for attention-deficit/hyperactivity disorder (ADHD)) and AKLT02 (late-stage development for cognitive dysfunction in pediatric autism spectrum disorder

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(ASD)). Both potential medicines are designed to be prescribed by a physician and delivered through immersive-action video games on a smartphone or tablet. (Mar.)

Akili receives $20m in up-front payments, development and commercialization milestones up to $105m, plus substantial royalties on sales in Japan and Taiwan. Shionogi, which committed to a future equity purchase in Akili, will also help fund development costs and be responsible for filing regulatory submissions within the licensed territories. Akili will create and support a new R&D and commercial global access platform (which includes global product development activities, distribution, and technical support services) and also take on data collection and storage tasks in compliance with local laws regarding privacy and personal health information management. A game played on tablet devices, AKLT01 features mechanisms to act on neural systems and algorithms that regulate up or down stimulus of the prefrontal cortex (an area of the brain known to play a key role in cognitive function). In August 2018 Akili submitted a 510(k) filing for ALKT01 for pediatric ADHD and expects FDA approval in the coming months. AKLT02 uses the same sensory and motor stimuli as AKLT01, but adapted to suit the ASD indication. The company expects to present at a conference in May results from a pilot randomized controlled trial evaluating AKLT02 in high-functioning children with ASDs.

CORVIA MEDICAL INC.
EDWARDS LIFESCIENCES CORP.

Edwards Lifesciences Corp. invested $35m in cardiovascular device maker **Corvia Medical Inc.** (formerly known as DC Devices) and gained the exclusive option to acquire the firm. (Mar.)

Ten-year-old Corvia will use the money to complete the REDUCE LAP-HF II pivotal clinical trial of its *InterAtrial Shunt Device* (*IASD*). Should the product go to market, it would be the first available transcatheter device for treating heart failure with preserved and mid-range ejection fraction. *IASD* works by providing continuous and dynamic decompression of the left atrium to reduce symptoms and slow the progression of heart failure. The device gained the CE Mark three years ago. Concurrently, Edwards acquired certain assets of **Mitralign**, which is developing a transcatheter annuloplasty system for treating functional mitral and tricuspid regurgitation.

MICRO INTERVENTIONAL DEVICES INC.
OSCOR INC.

Oscor Inc. granted **Micro Interventional Devices Inc.** (MID) non-exclusive global rights to its patented catheter technology, while Oscor gets exclusive manufacturing rights to MID's *MIA* (*Minimally Invasive Annuloplasty*) devices. (Mar.)

The collaboration leverages both firms' strengths and resources with which to develop and commercialize new products to treat structural heart disease. MID is currently conducting the STTAR clinical trial evaluating *MIA*'s safety and efficacy in the percutaneous treatment of tricuspid and mitral regurgitation. Concurrent with the alliance, Oscor led MID's $20m Series D round in which existing shareholders, including Originate Ventures, LifeSciences Greenhouse, and Ben Franklin Venture Partners, participated. In the financing, MID's debt will convert into Series D preferred shares. Oscor's CEO Thomas Osypka joins the company's board.

FINANCINGS

APOLLO ENDOSURGERY INC.

Apollo Endosurgery Inc. (minimally invasive devices for bariatric and gastrointestinal procedures) entered into a credit facility with Solar Capital. The company borrowed $35m initially and could get another $15m subject to further credit approval. The loan bears interest at LIBOR plus 7.5% and principal payments will begin after a 24-month interest-only period until maturity on September 1, 2023. Apollo used $22.4m of the proceeds to pay off the remainder of an existing senior secured credit facility. (Mar.)

SHOCKWAVE MEDICAL INC.

Concurrent with its IPO, cardiovascular device maker **ShockWave Medical** grossed $10m in a private placement of 588k common shares at $17 each to **Abiomed**. (Mar.)

SHOCKWAVE MEDICAL INC.

ShockWave Medical Inc. netted $90.1m through its initial public offering of 5.7 million common shares at $17 each on the Nasdaq. The company planned to sell 5 million shares between $14 and $16. (Mar.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Canaccord Genuity Inc.; Morgan Stanley & Co.; Wells Fargo Securities LLC

TITAN MEDICAL INC.

Titan Medical Inc. (robotic system for minimally invasive surgery) grossed $26.7m through the overnight marketed offering of 8.46 million units (including full exercise of the overallotment) at $3.40. Each unit consists of one common share and one five-year warrant to buy a share at $4. The company will use the proceeds for ongoing development of its *SPORT* surgical system. (Mar.)

Investment Banks/Advisors: Bloom Burton & Co.

PHARMACEUTICALS

MERGERS & ACQUISITIONS

BIOGEN INC.
NIGHTSTAR THERAPEUTICS PLC

Biogen Inc. is paying $877m in cash ($25.50 per share; a 70% premium) to acquire ophthalmic-focused **Nightstar Therapeutics PLC** (Biogen is valuing the deal at around $800m on a fully diluted basis, after factoring in anticipated transaction expenses and cash at closing.) (Mar.)

The acquisition accelerates Biogen's entry into the ophthalmology space, moving the company beyond its key areas of neurological, rare, and autoimmune diseases. Nightstar is developing adeno-associated virus (AAV) treatments for inherited retinal disorders. Its lead program is Phase III NSR-REP1 for choroideremia and designed to produce the REP1 protein inside the eye. Data from the trial is expected in H2 2020. Biogen also gains Phase I/II NSR-RPGR for X-linked retinitis pigmentosa. This candidate can potentially slow down or even halt retinal degeneration of photoreceptors and restore vision. NSR-REP1 and NSR-RPGR are both comprised of an AAV vector administered by subretinal injection. Nightstar's pipeline also includes preclinical assets for Stargardt's disease, Best disease, and retinitis pigmentosa. The acquisition comes just three months after Biogen pulled the plug on a mid-2015 deal with **Applied Genetic Technologies** following a failed Phase I/II trial of AGT's X-linked retinoschisis (XLRS) gene therapy program. Investment Banks/Advisors: Goldman Sachs & Co. (Biogen Inc.); Centerview Partners LLC; Jefferies & Co. Inc. (Nightstar Therapeutics PLC)

ONCTERNAL THERAPEUTICS INC.
GTX INC.

Oncternal Therapeutics Inc. will reverse merge through a stock-for-stock transaction with fellow cancer drug developer **GTx Inc.** The resulting firm will take the Oncternal name and GTx's Nasdaq listing, and will be 75% owned by current Oncternal shareholders. (Mar.)

The combined entity's pipeline will consist of Oncternal's three lead projects: cirmtuzumab (anti-ROR1 mAb in Phase I/II for chronic lymphocytic leukemia and mantle cell lymphoma), TK216 (Phase I alone and together with vincristine for Ewing sarcoma), and a preclinical ROR1-targeted CART therapy for blood and solid tumors. It will also continue developing GTx's preclinical SARD (selective androgen receptor degrader) program for castration-resistant prostate cancer. GTx stockholders are eligible to receive contingent value rights (CVRs) good for 50% of the net proceeds from the grant, transfer of rights, or sale of

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the SARD technology, plus royalties on sales by the combined company of any SARD products. The companies note that GTx employees will not be retained post-merger, but the board of directors of the new firm will have seats reserved for current GTx board members Robert Wills, PhD (GTx executive chairman) and Michael Carter, MD. For GTx, the deal comes about six months after the company announced that its lead selective androgen receptor modulator candidate enobosarm failed a Phase II stress urinary incontinence trial (after previously failing in breast cancer). Shortly after, GTx announced it would explore strategic alternatives for the firm. Investment Banks/Advisors: Aquilo Partners Inc. (GTx Inc.); Piper Jaffray & Co. (Oncternal Therapeutics Inc.)

SORRENTO THERAPEUTICS INC.
Scilex Pharmaceuticals Inc.
SEMNUR PHARMACEUTICALS INC.

Sorrento Therapeutics Inc.'s **Scilex Pharmaceuticals Inc.** subsidiary has agreed to merge with private **Semnur Pharmaceuticals Inc.** to form a combined company focused on non-opioid pain medications. Previously holding a 77% ownership in Scilex (gained mostly through a 2016 transaction), Sorrento will have a 58% stake in the combined company, which will be known as **Scilex Holding Co.** (Mar.)

Sorrento is interested in leveraging the potential of Semnur's sole pipeline candidate SP102 (lidocaine injectable gel formulation) in Phase III (initiated in January 2018) for lumbar radicular pain (sciatica) with Scilex's advanced patch adhesion technology to deliver non-opioid pain drugs. Sorrento will pay up-front consideration of $67m (including a cash payment of approximately $12.4mm, plus $55m (47 million shares) in stock consideration) and up to $280m in earn-outs contingent upon the achievement of certain milestones, including the first approval by the FDA of an NDA for a Semnur product and the achievement of certain net sales of a Semnur product. Semnur's SP102--which gained Fast Track status from the FDA (December 2017) and has the potential to be the first non-opioid corticosteroid epidural product to treat sciatica--fits in nicely with Scilex's own topical *ZTlido* (lidocaine 1.8%), which received FDA approval in February 2018 for pain associated with post-herpetic neuralgia (post-shingles pain) and launched in the US in October 2018. Back in August 2016, **Scintilla Pharmaceuticals** (another division of Sorrento) attempted to buy Semnur for up to $48mm, but that transaction was terminated in October 2017.

ALLIANCES

AFFIBODY AB
ALEXION PHARMACEUTICALS INC.

Alexion Pharmaceuticals Inc. and **Affibody AB** penned a co-development deal surrounding the latter's anti-FcRn molecule ABY039. (Mar.)

ABY039 is a bivalent antibody mimetic targeting the neonatal Fc receptor (FcRn) and is in Phase I trials for rare immunoglobulin (IgG)-mediated autoimmune diseases. Affibody used its *Albumod* albumin-binding domain technology to design the compound in such a way that its circulatory half-life is longer than antibodies directed at FcRn. ABY039 is smaller than a typical antibody and can be delivered via low-volume subcutaneous administration at home by the patient. Alexion paid $25m up front for rights to co-develop the candidate with Affibody and could hand over an additional $625m in development and sales milestones, plus tiered low double-digit royalties. Affibody retains a co-promotion option in the US and will head up development of ABY039 for an undisclosed indication. The deal brings Alexion its second anti-FcRn project. In September, the company paid $400m up front (and committed to another $800m in earn-outs) to acquire **Syntimmune** and its lead FcRn candidate SYNT001 (renamed ALXN1830), which is in Phase Ib/IIa trials for warm autoimmune hemolytic anemia and pemphigus vulgaris or pemphigus foliaceus. Both candidates put Alexion in a good position in terms of its competition in the space. Other firms developing anti-FcRn projects include **UCB** and its rozanolixizumab and **Argenx** with efgartigimod, both in trials for myasthenia gravis and idiopathic thrombocytopenic purpura.

ALEXION PHARMACEUTICALS INC.
ZEALAND PHARMA AS

Alexion Pharmaceuticals Inc. licensed exclusive global rights to develop and sell up to four peptide therapeutics for complement-mediated diseases under a deal with **Zealand Pharma AS**. (Mar.)

Uncontrolled activation of the complement pathway is the cause of a number of serious diseases. Under terms of the current collaboration, Zealand will lead discovery of subcutaneously delivered peptide therapies through preclinical studies, and Alexion will then take over to conduct IND activities and further clinical development, with exclusive global rights to commercialize resulting candidates. For rights to the first target, Alexion pays $25m up front and makes a $15m equity investment (at an undisclosed premium). Zealand could also receive up to $115m in development milestones, $495m in sales milestones, and high-single to low-double digit royalties. (*Strategic Transactions* estimates 7-29%). If Alexion chooses to exercise an option on the remaining three targets, it will make option exercise payments of $15m per project, plus milestones and royalties (at a lower amount than the original target). Alexion already has two complement pathway inhibitors on the market, *Soliris* (eculizumab) and *Ultomiris* (ravulizumab), both for paroxysmal nocturnal hemoglobinuria. (*Soliris* is also approved for atypical hemolutic uremic syndrome.) The deal is the second announced in the same day for the company. It also announced a partnership with **Affibody** through which Alexion licensed rights to the bivalent antibody mimetic ABY039, which is in Phase I for rare immunoglobulin G (IgG)-mediated autoimmune diseases. For that collaboration, it paid $25m up front and committed to up to $625m in milestones.

AMBRX INC.
BEIGENE LTD.

Ambrx Inc. and **BeiGene Ltd.** will use Ambrx's site-specific conjugation platforms to discover and develop next-generation biologic therapies for cancer. (Mar.)

The partners will leverage Ambrx's Expanded Genetic Code platforms that incorporate non-natural amino acids into proteins in E. coli (the *ReCODE* (*Reconstituting Chemically Orthogonal Directed Engineering*) technology) and CHO cells (*EuCODE*) for site-specific protein modification and bio-conjugation. *ReCODE* creates long-acting therapeutic peptides and proteins, and modified antibody and bispecific fragments, while *EuCODE* creates larger complex proteins with function that is dependent on post-translational modification. BeiGene gets worldwide rights to develop and sell resulting bioconjugate candidates, and in turn pays Ambrx $10m up front, $19m if BeiGene chooses to develop additional projects, and up to $446m in development, regulatory, and commercialization milestones, plus tiered royalties. Ambrx adds BeiGene to a growing list of partners who use the company's conjugation platforms for drug discovery including **Astellas Pharma**, **BMS**, **Eli Lilly** (its Elanco animal health division), and **Zhejiang Medicine**.

IMMUNEXT INC.
ELI LILLY & CO.

In a deal that enhances its immunology pipeline, **Eli Lilly & Co.** agreed to pay **ImmuNext Inc.** $40m up front for exclusive global rights to develop and sell one of ImmuNext's preclinical immunometabolism targets. (Mar.)

Under terms of the deal, which carries a three-year research term, Lilly could hand over up to an additional $565m in development and sales milestones, plus royalties ranging from the mid-single to low-double

digits. (*Strategic Transactions* estimates 7-29%.) The partners will work together to advance the undisclosed first-in-pathway antibody that has been discovered to target the metabolism of lymphocytes and reprogram (rather than suppress) the immune system as a potential therapy for autoimmune diseases. The project will be added to Lilly's immunology pipeline that currently houses more than ten candidates in the space, in trials ranging from Phase I to Phase III. The collaboration brings ImmuNext its fourth major partner. **Sanofi**, **Roche**, and **Janssen Biotech** are all also enhancing their immunotherapy pipelines through licensing deals with the company. Including the current agreement with Lilly, ImmuNext is now eligible for a total of $1.6bn in milestone payments from its partners.

LABORATOIRES THEA SAS
OLIX PHARMACEUTICALS INC.

OliX Pharmaceuticals Inc. licensed **Laboratoires Thea SAS** rights to develop and commercialize OLX301A in Europe, the Middle East, and Africa. (OliX retains rights in the US and Asia.) (Mar.)

OliX received €2m ($2.26m) up front and could get development milestones and sales royalties. OLX301A is a preclinical gene expression inhibitor aimed at both dry and wet age-related macular degeneration. The compound is based on OliX's cell penetrating asymmetric siRNA (cp-asiRNA) technology, which allows for RNA to be delivered into the cells without a delivery vehicle. The cp-asiRNA platform is ideal for use in ophthalmic therapies because it can eliminate the potential for side effects that exist when using traditional siRNA technology. OliX expects a Phase I trial to commence this year.

LG GROUP
LG Chem Life Sciences Co.
PDC*LINE PHARMA

PDC*line Pharma granted **LG Chem Life Sciences Co.** exclusive rights to develop and commercialize its *PDC*lung* cancer vaccine in South Korea, with options to expand to additional Asian countries in the future. (Mar.)

Under terms of the deal, PDC gets money up front and up to €108m ($123m) in development and regulatory milestones, plus sales royalties. *PDC*lung* is made up of a cell line containing plasmacytoid dendritic cells (*PDC*line*) that is loaded with HLA-A2 restricted peptides derived from six shared tumor antigens. The vaccine is indicated for advanced-stage NSCLC patients and will enter a Phase Ib/IIa trial this year. The collaboration expands LG Chem's immuno-oncology portfolio and enhances global visibility for PDC*line. The company will continue developing *PDC*lung* in the US, EU, and all other ex-Asia territories.

NICOX SA
OCUMENSION THERAPEUTICS

Nicox SA licensed **Ocumension Therapeutics** exclusive rights to develop and commercialize the antihistamine *Zerviate* (cetirizine; formerly AC170) ophthalmic solution 0.24% for allergic conjunctivitis in China, Hong Kong, Macau and Taiwan. (Mar.)

For the rights, Ocumension will pay up to €17m ($19.2m) in development and commercial milestones, plus 5-9% sales royalties. The deal comes just three months after the two firms penned an agreement in which Nicox granted Ocumension exclusive rights to develop and commercialize the glaucoma candidate NCX470 in the same Asian territories as the current agreement. FDA approved *Zerviate* is the first available topical cetirizine formulation for treating ocular itching associated with allergic conjunctivitis. Under a 2017 tie-up, **Eyevance Pharmaceuticals** has rights to sell the product in the US; a summer 2019 launch is expected.

NIPPON SHINYAKU CO. LTD.
ZOGENIX INC.

Nippon Shinyaku Co. Ltd. licensed exclusive Japanese commercialization rights to **Zogenix Inc.**'s *Fintepla* (fenfluramine; formerly known as ZX008) for Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS), both rare, childhood-onset epilepsies. (Mar.)

Zogenix first gained the compound (then known as *Brabafen*) through its 2014 acquisition of rare epilepsy drug developer **Brabant**. Nippon will pay Zogenix $20m up front (most already paid at signing and the rest to come over the next two years) in addition to future regulatory and sales-based milestones. Zogenix will supply product to Nippon in exchange for a tiered transfer price based on Zogenix's manufacturing costs, as well as the annual net sales of *Fintepla* in Japan. Zogenix retains responsibilities for completing clinical development programs, including a global Phase III trial in LGS and those supporting planned NDA submissions in Japan for both DS and LGS. Last month, Zogenix filed both a rolling NDA with the FDA and an MAA with the EMA in the DS indication (for which *Fintepla* has a 99% likelihood of approval (16% above average)). The European filing was accepted, and company expects an FDA PDUFA decision regarding the filing status of its NDA by August 2019; an EMA approval decision is anticipated in Q1 2020. The candidate has orphan status in the US and the EU in both indications.

NOVARTIS AG
SECURA BIO INC.

Secura Bio Inc. licensed worldwide rights to **Novartis AG**'s multiple myeloma candidate *Farydak* (panobinostat). (Mar.)

Indicated for previously treated relapsed or refractory multiple myeloma patients, *Farydak* is an oral histone deacetylase (HDAC) inhibitor used in combination with proteasome inhibitor chemotherapeutics (such as bortezomib) and corticosteroids (including dexamethasone). Already cleared by the EMA (in 2015) and in over 50 other countries in this indication, *Farydak* also received accelerated approval from the FDA (which had earlier voted against approval) in 2015 after data showed the drug has an effect on an endpoint reasonably likely to predict clinical benefit to patients. To gain full FDA approval, Novartis is required to conduct confirmatory clinical trials and submit additional information verifying and describing the clinical benefit of *Farydak* and demonstrating its ability to improve survival or disease-related symptoms. *Farydak* is also in development for solid and hematological cancers. Under a 2017 deal, **Midatech Pharma** gained global rights to the compound for diffuse intrinsic pontine glioma (DIPG), an ultra-rare childhood brain cancer, and potentially glioblastoma (GBM); indications for which the therapy is in preclinical development. It's unclear if Midatech still retains these rights. Founded earlier this year to focus on commercializing oncology therapies, Secura recently closed a $145m Series A equity/debt round. So far, *Farydak* is its only disclosed asset.

ONCODESIGN SA
SERVIER SA

Oncodesign SA and **Servier SA** agreed to collaborate on the research and development of leucine-rich repeat kinase 2 (LRRK2) inhibitors in Parkinson's disease (PD) using Oncodesign's *Nanocyclix* medicinal chemistry technology. (Mar.)

The LRRK2 inhibitors are derived from Oncodesign's *Nanocyclix* platform, a technology that provides access to a kinase inhibitor library of over 8k macrocycles, a type I kinase inhibitor. Used for designing, synthesizing, and optimizing this type of macrocyclic small molecule, the *Nanocyclix* platform can be applied to numerous therapeutic targets, but in particular kinases, which combine high strength and selectivity with a low molecular weight and highly attractive physical and chemical properties. LRRK2 inhibitors have the potential to directly impact PD progression, unlike currently available therapies that merely alleviate symptoms. Servier will entirely fund the research program, which will be conducted by Oncodesign (at its own site) up to the selection of preclinical candidates. Servier has an exclusive worldwide licensing option, which can be exercised following IND status. In exchange, Oncodesign gets €3m ($3.4m) up front; up to €320m in milestones (including payments through validation of a candidate for Phase I); and €3m in annual research funding. The deal boosts Servier's neuro pipeline--which already has programs in neurodegenerative and psychiatric diseases, stroke, and autism--and frees Oncodesign to work on its own *Nanocyclix*-based development programs, including RIPK2 (auto-immune disease), ALK1 (tumor angiogenesis), and MNK1 (cancer). Oncodesign has a 2012 *Nanocyclix* partnership with **Ipsen** in PD as well as similar deals in various therapeutic areas with other companies.

PETRA PHARMA CORP.
TAKEDA PHARMACEUTICAL CO. LTD.

Takeda Pharmaceutical Co. Ltd. granted **Petra Pharma Corp.** global rights to develop, manufacture, and sell the PI3K alpha/beta inhibitor serabelisib (PETRA06) for all indications (excluding certain undisclosed rare diseases previously out-licensed by Takeda). The deal also includes rights to two additional PI3Ka inhibitors. (Mar.)

Financial terms of the deal were not disclosed. Petra is developing PI3K inhibitors for cancer and other diseases based on the research of **Weill Cornell**'s Dr. Lewis Cantley and **Harvard Medical School**'s Dr. Nathanael Gray. Dr. Cantley and his researchers found that PI3K mediates the cellular actions of insulin, and that current PI3K inhibitors have been shown to elevate glucose levels and raise serum insulin, thereby re-activating PI3K in tumors and allowing the cancer to survive. Cantley's approach combines PI3K inhibitors with ketogenic diet or glucose-lowering agents to stop the glucose-insulin feedback loop. Petra plans to commence Phase Ib/II trials with serabelisib later this year for PIK3CA-mutated solid tumors. Takeda originally gained the candidate through its 2011 acquisition of Intellikine. Serabelisib is in Phase II studies for endometrial and renal cancers, and Phase I for esophageal and breast tumors.

PFIZER INC.
VIVET THERAPEUTICS

Vivet Therapeutics and **Pfizer Inc.** are teaming up to develop Vivet's preclinical VTX801 gene therapy for Wilson disease. (Mar.)

Pfizer paid $51m (€45m) up front and gets a 15% equity stake in Vivet. The Big Pharma now holds the option to purchase the company outright following the delivery of certain data from the Phase I/II clinical trial for VTX801. Pfizer could shell out $635.8m in the form of an option exercise payment and clinical development, regulatory, and commercial milestones. A senior executive, Monika Vnuk, MD, joins Vivet's board. VTX801 uses a modified AAV vector to deliver the gene as a treatment for Wilson disease, which is a rare liver disorder that may result in fatal copper poisoning because of a defect in the P-type adenosine triphosphatase gene encoding the copper transporting P-type ATPase. Current therapies have sub-optimal efficacy or significant side effects. Vivet and Pfizer seek to create a new option for Wilson disease patients by creating a therapeutic that addresses the underlying cause of the disease using a high-activity ATP7B truncated transgene that can help restore copper homeostasis. There have been several high-priced deals in the gene therapy space just this year. In January **Janssen Pharmaceuticals** and **MeiraGTx** teamed up in a potential $440m agreement to create gene therapies for inherited retinal diseases. In February Roche announced plans to acquire public gene therapy firm **Spark Therapeutics** for $4.8bn. Then earlier this month, Biogen penned an $800m deal to acquire ophthalmic gene therapy developer **Nightstar Therapeutics**. Gene therapies are getting a lot of attention because they offer the potential for a long-lasting and even permanent effect via a one-time treatment.

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STRIDEBIO INC.
TAKEDA PHARMACEUTICAL CO. LTD.

StrideBio Inc. will use its adeno-associated virus (AAV) capsid technology to discover novel gene therapies in the neurology space for **Takeda Pharmaceutical Co. Inc.** (Mar.)

Takeda hands over $30m in up-front payments and near-term preclinical milestones, plus up to $680m in additional development and sales milestones, as well as royalties. StrideBio's "STRucture Inspired DEsign" approach engineers novel synthetic AAV capsids that can evade neutralizing antibodies and produce vectors with enhanced potency and tissue tropism. StrideBio will develop the AAV capsids, carry out preclinical studies, and manufacture preclinical candidates. The partners' initial focus is on Fredrich's Ataxia, and the deal includes two additional undisclosed targets. Takeda is responsible for all clinical development and global commercialization.

FINANCINGS

ALDEYRA THERAPEUTICS INC.

Aldeyra Therapeutics Inc. (developing therapies for immune-mediated diseases including ophthalmic conditions, metabolic diseases, and cancer) entered into a non-dilutive term loan facility worth up to $60m with Hercules Capital. Aldeyra will get an initial $5m. It can receive three additional term loan advances of up to $15m upon the achievement of certain funding conditions prior to September 30, 2019, March 31, 2020 and March 31, 2021. The final loan advance of up to $10m is subject to approval by Hercules' investment committee. The loan bears interest at an annual rate equal to the greater of 9.10% and the prime rate plus 3.10%. The interest-only period is for 24 months, with an option to extend to 36 months based on certain circumstances. The financing is concurrent with Aldeyra's announcement of positive results from the Phase III ALLEVIATE trial of 0.25% and 0.5% reproxalap topical ophthalmic solution in patients with allergic conjunctivitis. (Mar.)

ALPHAEON CORP.
Evolus Inc.

Evolus Inc. (medical aesthetics) secured a two-tranche $100m senior debt facility from Oxford Finance. The company drew down $75m at closing and the remainder will be available at the company's option no later than September 30, 2020, upon achieving specified minimum net sales milestones. The credit facility will mature on March 1, 2024 and bears an annual interest rate equal to the greater of 9.5%, or the 30-day US LIBOR rate plus 7.0%. Evolus is required to make interest-only payments through April 2022. Just last month, the company gained FDA approval for its *Jeuveau* (prabotulinumtoxinA-xvfs) neurotoxin with indications in facial aesthetics, including moderate to severe glabellar (frown) lines. (Mar.)

Investment Banks/Advisors: Cantor Fitzgerald & Co. (Evolus Inc.)

APELLIS PHARMACEUTICALS INC.

Apellis Pharmaceuticals Inc. (drug development based on inhibition of the complement system) netted $110m through a public offering of 6.9 million common shares (including the overallotment) at $17. Funds will support continued development of lead candidate APL2 for a variety of indications including geographic atrophy and paroxysmal nocturnal hemoglobinuria (both in Phase III), and wet AMD, autoimmune hemolytic anemia, and complement-dependent neuropathies (all in Phase II). (Mar.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Citigroup Inc.; Cowen & Co. LLC; JP Morgan Chase & Co.

APTEVO THERAPEUTICS INC.

Aptevo Therapeutics Inc. (blood disease and cancer treatments) netted $20m through a follow-on public offering. The company sold 19.8 million common shares at $0.99 (together with five-year warrants to purchase 19.8 million common at $1.30), and also issued pre-funded warrants to purchase 2.15 million common at $0.98 per warrant (plus common share warrants to buy 2.15 million shares at $1.30). (Mar.)

Investment Banks/Advisors: Piper Jaffray & Co.

ASCENDIS PHARMA AS

Rare disease therapies developer **Ascendis Pharma AS** netted $470m through the follow-on public offering of 4.17 millionAmerican Depositary Shares (each ADS represents one ordinary share) at $120 each. The company plans to use the proceeds for clinical development, regulatory, and commercialization activities for its *TransCon* growth hormone; for development of other rare disease endocrinology programs, including *TransCon PTH* and *TransCon CNP*; and to develop cancer therapeutics. (Mar.)

Investment Banks/Advisors: Canaccord Genuity Inc.; Cantor Fitzgerald & Co.; Credit Suisse Group; Evercore Partners; JP Morgan & Co.; Morgan Stanley & Co.; Wedbush PacGrow Life Sciences; Wells Fargo Securities LLC

BIO-PATH HOLDINGS INC.

Bio-Path Holdings Inc. (using its *DNAbilize* delivery platform to develop RNAi nanoparticle drugs for cancer) netted $17.2m in a registered direct offering of 712,910 common shares at $25.95 (a 101% premium to the ten-day pre-announcement market average). A week prior to the RDO, Bio-Path announced positive interim data analysis of a Phase II trial with lead candidate prexigebersen in acute myeloid leukemia. This news caused the company's stock to jump from $4.62 per share to $38.86 in just two days. The day of the offering, trading closed at $35.13. (Mar.)

Investment Banks/Advisors: HC Wainwright & Co.

BIOHAVEN PHARMACEUTICAL HOLDING CO. LTD.

Through a private placement, **Biohaven Pharmaceutical Holding Co. Ltd.** issued 2.5k preferred shares at $50.1k ($125m) to Royalty Pharma. The financing was concurrent with and will help support the Biohaven's $105m purchase of **GW Pharmaceuticals**'s rare pediatric disease priority review voucher (PRV; awarded to GW upon the June 2018 FDA approval of its *Epidiolex* (cannabidiol) for rare childhood seizures). Biohaven will use the PRV to expedite regulatory review for its own Phase III migraine candidate rimegepant (*Zydis* orally disintegrating tablet (ODT) formulation), a calcitonin gene-related peptide receptor antagonist, for which an NDA is expected in Q2 2019. Biohaven may draw down an additional $75m upon the FDA's acceptance of the NDA for rimegepant. (Mar.)

BIOHAVEN PHARMACEUTICAL HOLDING CO. LTD.
GW PHARMACEUTICALS PLC

GW Pharmaceuticals PLC agreed to sell **Biohaven Pharmaceutical Holding Co. Ltd.** its rare pediatric disease priority review voucher (PRV) for $105m. (Mar.)

CELLULAR BIOMEDICINE GROUP INC.

Cellular Biomedicine Group Inc. netted $16.3m through a public offering of 1 million common shares at $17. The company is developing immunotherapies for cancer and stem cell therapies for degenerative diseases; its most advanced project is *ReJoin*, a human adipose-derived mesenchymal progenitor cell (haMPC) therapy for knee osteoarthritis, which completed Phase IIb. (Mar.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Robert W. Baird & Co. Inc.

CURIS INC.

Curis Inc. agreed to sell some of the royalties it receives from sales of the basal cell carcinoma drug *Erivedge* (vismodegib) to funds managed by Oberland Capital Management. The company could receive up to $135.7mm, including $65m up front and an additional $70.7m if future royalties exceed pre-defined thresholds. (Mar.)

CYMABAY THERAPEUTICS INC.

CymaBay Therapeutics Inc. (developing treatments for liver and other chronic diseases) netted $108m through the public sale of 9.2 million common shares

(including the overallotment) at $12.50. Funds will support continued development of lead candidate seladelpar, in Phase III for primary biliary cholangitis and Phase II for nonalcoholic steatohepatitis. (Mar.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Citigroup Inc.; Evercore Partners; Oppenheimer & Co. Inc.; Roth Capital Partners

DERMIRA INC.

Dermira Inc. (therapeutics for dermatology indications) netted $122.2m in a public offering of 9.8 million shares at $13.25. The company will use the proceeds to support ongoing commercialization activities for *Qbrexza* (glycopyrronium tosylate), a topical acetylcholine receptor antagonist launched late last year in the US for primary axillary hyperhidrosis. It will use some funds to advance R&D programs, including a planned Phase III trial for interleukin 13 antagonist lebrikizumab in atopic dermatitis expected by the end of 2019. Through a deal signed last month, Dermira stands to get up to $1.4bn should **Almirall** exercise its option for European rights to lebrikizumab. (Mar.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Citigroup Inc.; Cowen & Co. LLC; Guggenheim Partners LLC; HC Wainwright & Co.; Needham & Co. Inc.

GENFIT SA

Genfit SA (therapies for liver and metabolic diseases; also has a nonalcoholic steatohepatitis diagnostic in development) netted $11.6m through its initial public offering in the US of 6.15 million ordinary shares at $20.32. The company will list on the Nasdaq Global Select Market; it already lists on Euronext Paris. (Mar.)

Investment Banks/Advisors: Barclays Bank PLC; Bryan Garnier & Co.; HC Wainwright & Co.; Leerink Partners LLC; Natixis Bleichroeder Inc.; Roth Capital Partners

GENFIT SA

Genfit SA (drugs and diagnostics for metabolic and liver-related diseases) netted $9.4m through a private placement of 500k ordinary shares at €18 ($20.32; a 26% discount). The PIPE closed concurrent with Genfit's $116m initial public offering of its ADSs on the US Nasdaq. The company's shares are already listed on Euronext Paris. (Mar.)

HORIZON PHARMA PLC

Horizon Pharma PLC netted $327.7m in a follow-on public offering of 14 million ordinary shares (including the overallotment) at $24.50. The company will use the proceeds (along with cash on hand) to repay $550m in outstanding debt, including a portion of the outstanding principal amount of its 6.625% senior notes due 2023. Horizon also concurrently amended an existing credit agreement securing loan commitments for an additional $200m. (Mar.)

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

IMV INC.

IMV Inc. (formerly Immunovaccine; immuno-oncology) netted $Cdn29m ($20.6m) through a public offering of 5.4m common shares (including partial exercise of the overallotment) at $Cdn5.45. Proceeds will fund development of DPX-Survivac, a T-cell-activating immunotherapy, in combination with **Merck**'s *Keytruda* (pembrolizumab) for advanced or recurrent bladder, liver (hepatocellular carcinoma), ovarian or non-small-cell lung cancers, as well as tumors that are positive for the microsatellite instability high biomarker. (Mar.)

Investment Banks/Advisors: B. Riley FBR Inc.; Raymond James & Associates Inc.; Wells Fargo Securities LLC

INFINITY PHARMACEUTICALS INC.

HealthCare Royalty Partners (HCR) will pay **Infinity Pharmaceuticals Inc.** $30m up front and up to $20m down the line in exchange for certain royalty payments on global sales of *Copiktra* (duvelisib), an oral PI3K inhibitor for relapsed or refractory chronic lymphocytic leukemia/small lymphocytic leukemia and relapsed or refractory follicular lymphoma. (Mar.)

LIGAND PHARMACEUTICALS INC.

Ligand Pharmaceuticals Inc. agreed to sell Royalty Pharma the intellectual property rights, including the royalty stream on worldwide net sales, to *Promacta* (eltrombopag) for $827m in cash. (Mar.)

MATINAS BIOPHARMA HOLDINGS INC.

Matinas Biopharma Holdings Inc. (treatments for cardiovascular, infectious, and metabolic diseases) netted $28.2m through a public offering of 27.3 million common shares at $1.10. Funds will support development activities including work on lead candidate MAT9001 for severe hypertriglyceridemia and continued development of the company's lipid nano-crystal (LNC) intracellular delivery technology. (Mar.)

Investment Banks/Advisors: BTIG LLC

MERSANA THERAPEUTICS INC.

Mersana Therapeutics Inc. (antibody-drug conjugates for cancer) netted $92m through a public offering of 24.4 million common shares (including the overallotment) at $4. Funds will support continued development of XMT1536, a dolaflexin ADC targeting NaPi2b-expressing tumors that is in Phase I for ovarian and non-small cell lung cancers. Money will also help the company progress preclinical projects into clinical trials, and advance early platform development activities. (Mar.)

Investment Banks/Advisors: SVB Financial Group; Wedbush PacGrow Life Sciences

MYOKARDIA INC.

Cardiovascular disease-focused **MyoKardia Inc.** netted $236.1m in a follow-on public offering of 4.93 million common shares at $51 each. The company will use the proceeds to support ongoing clinical trials and regulatory and commercial activities for its mavacamten for treating obstructive hypertrophic cardiomyopathy (HCM); to fund development of mavacamten in non-obstructive HCM and MYK491 in targeted segments of systolic heart failure; and for earlier stage pipeline development. (Mar.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Cowen & Co. LLC; Credit Suisse Group; Wedbush PacGrow Life Sciences; Wells Fargo Securities LLC

ORAGENICS INC.

Antibiotics developer **Oragenics Inc.** netted $11.6m through a follow-on offering of 16.67 million common shares at $0.75 each. The company also issued Series 1 warrants to buy 8.33 common shares at an exercise price of $0.75; the warrants expire on the earlier of 18 months or 21 trading days following the release of topline data related to its Phase II trial of AG013 for oral mucositis (expected in early 2020). It also issued 8.33 million five-year Series 2 warrants to buy a share at $0.90. Oragenics will use the proceeds for ongoing clinical development of AG013, and preclinical studies of its lantibiotics program. (Mar.)

Investment Banks/Advisors: HC Wainwright & Co.

PORTOLA PHARMACEUTICALS INC.

Portola Pharmaceuticals Inc. entered into a $125m loan agreement with Athyrium Capital Management and HealthCare Royalty Partners. Under terms of the non-dilutive financing, Portola can draw down the funds in two equal tranches (each carrying interest at 9.75%): the first $62.5m will be available when the agreement closes and the second is subject to certain conditions (regulatory approval in Europe of *Andexxa* (coagulation factor Xa (recombinant), inactivated-zhzo), approved in the US for anticoagulation reversal in patients treated with rivaroxaban or apixaban, and if sales of the drug hit at least $50m for the three-quarter-period ending September 30, 2019). Proceeds from loan will support commercialization of *Andexxa*. (Mar.)

Investment Banks/Advisors: Cowen & Co. LLC

PRECISION BIOSCIENCES INC.

Gene editing firm **Precision BioSciences Inc.** filed for its initial public offering. (Mar.)

Investment Banks/Advisors: Barclays Bank PLC; Goldman Sachs & Co.; JP Morgan Chase & Co.; Jefferies & Co. Inc.

RESTORBIO INC.

ResTORbio Inc. (developing therapies to prevent or treat age-related diseases) netted $47m through the follow-on public offering of 7.2 million common shares at $6.95 each. The company will use some of the proceeds for R&D activities and related costs, manufacturing, infrastructure expansion, and potential acquisitions. (Mar.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Guggenheim Partners LLC; SVB Financial Group; Wedbush PacGrow Life Sciences

SAREPTA THERAPEUTICS INC.

Sarepta Therapeutics Inc. netted $365.7m through a public offering of 2.6 million common shares at $144. Proceeds will support continued development, commercialization, and business activities pertaining to the company's pipeline of RNA targeted therapies and gene therapies for Duchenne muscular dystrophy, 5 Limb-girdle muscular dystrophy diseases, Charcot-Marie-Tooth, MPS IIIA, Pompe, and other CNS-related conditions. (Mar.)

Investment Banks/Advisors: Goldman Sachs & Co.; Morgan Stanley & Co.

TG THERAPEUTICS INC.

TG Therapeutics Inc. (treatments for autoimmune diseases and B-cell malignancies) netted $24.1m through a public offering of 4.1 million common shares. Proceeds will go towards development of ublituximab (Phase III for blood cancers and multiple sclerosis) and umbralisib (Phase III in combination with ublituximab for blood cancers), and will also support general corporate needs. The offering was completed concurrent with a $60m loan agreement TG entered with Hercules Capital. (Mar.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.

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