DEAL-MAKING
The biopharma building blocks: acquiring, partnering, funding
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From Device Centric To Disease Management: Ascensia Commits To Deeper Role In Diabetes
ASHLEY YEO
Ascensia is en route to becoming a one-stop-shop for diabetes management solutions. A significant step toward these goals was taken in January, when the Swiss group completed a key China deal with a local CGM innovator, chief marketing and strategy officer Martin Lange explains to In Vivo.

Deal-Making Fires Up To Unlock Checkpoint Inhibitors’ Full Potential
MELANIE SENIOR
Merck & Co.’s Keytruda is already elbowing its way into the top 10 best-selling drugs. But it, and its expanding cohort of competitors, could be much bigger. Companies and investors are scrambling to identify the technologies that can unlock checkpoint inhibitors’ potential where they do not currently work. That activity is reflected across 2018’s licensing deals, M&A and financings.

VC Playbook: As China Looms, Sofinnova Partners Keeps The Faith In A Resilient Europe
WILLIAM LOONEY
In this first installment of VC Playbook, a new series profiling venture capital groups in biopharma and medtech, In Vivo talks to Antoine Papiernik, managing partner and chair of Sofinnova Partners – Europe’s largest and oldest VC devoted to the life sciences, with €2bn under management.

David Or Goliath: Where Is Innovation Winning Through?
LUCIE ELLIS
With both a big pharma and biotech leadership perspective, David Meeker talks to In Vivo about how smaller firms can fly solo in drug development, challenges effecting the innovative drug development sector in 2019 and the partnering environment for cell and gene therapy companies.
Throughout January, our readers have been voting for the top M&A transaction, financing round and alliance of 2018. Which companies have triumphed in the 11th annual In Vivo Deals Of The Year competition? Find out now on page 7.

For February, we have focused on deal-making; exploring alliances, acquisitions, partnership strategies and private financing trends. In Vivo has used its data sources to create an infographic timeline of venture capital investments in 2018. Alongside this, our February issue includes investor and biotech commentary on how more VC cash might impact deal-making activity this year.

Also, this month, Ascensia’s chief marketing and strategy officer Martin Lange chats with Ashley Yeo about the company’s recent agreement with China’s Zhejiang POC Tech and Ascensia’s plans to move beyond diabetes device technology into disease management. This major strategic move has seen Ascensia agree to become the exclusive distributor for POC Tech in 13 selected markets and take options over distribution rights in other countries.

Meanwhile, Melanie Senior explores the deal-making landscape around cancer vaccines and oncolytic viruses. In 2018, three oncolytic virus companies were snapped up by big pharmas seeking to expand their immuno-oncology portfolios and secure a lead or foothold in the checkpoint inhibitor space. And while cancer vaccines have, until now, largely disappointed, there were at least four cancer vaccine IPOs in 2018, including the largest in biotech’s history.

February also sees us launch a new regular feature, VC Playbook – a series profiling venture capital groups in biopharma and medtech. In this first installment, William Looney talks to Antoine Papiernik, managing partner and chair of Sofinnova Partners, Europe’s largest and oldest VC devoted to the life sciences, with €2bn under management.
Up-Front

SNAPSHOTS FROM FEBRUARY’S CONTENT

VC SNAPSHOT: A LOOK AT THE TRANSACTIONS FROM 2018 THAT MADE IT A RECORD-BREAKING YEAR FOR BIOTECH FUND RAISING.

PAGE 10

“GOOD TECHNOLOGY IS A GOOD TOOL, BUT WE NEED TO GO FURTHER AND LOOK AT HOW WE CAN HELP PATIENTS IN THEIR DAY-TO-DAY LIVES,” SAYS ASCENSIA’S MARTIN LANGE.

PAGE 12

THERE WERE AROUND FOUR CANCER VACCINE IPOS IN 2018, INCLUDING THE LARGEST IN BIOTECH’S HISTORY, MODERNA’S $600M HAUL.

PAGE 18

“There is no substitute for people who are motivated by the mission,” says David Meeker, CEO of KSQ Therapeutics. He discusses the company’s approach to partnering and the pros and cons of being a smaller biotech in the huge, competitive market of cancer drug development.

PAGE 30

“Europe has changed in the past two decades. It takes time to move away from a historic, culturally reinforced mentality that risk is bad and failure never allows for a fresh start,” says Antoine Papiernik, managing partner and chair of Sofinnova Partners, in the first installment of In Vivo’s new regular feature, VC Playbook.

PAGE 24
Medtechs Ready To Take Creative Approach To Deal-Making With An Eye On Start-Ups

Anyone supposing that global medtech deals have hit the buffers would have been otherwise enlightened at the LSX World Congress, in London, in February 2019. True, Brexit might see confidence take a short-term dip, health systems are fighting for budget and using their reimbursement spends ever-more-carefully, and the forthcoming Medical Device Regulation is painting a somewhat forbidding picture for would-be start-ups up and device innovators in the EU.

But a high-level panel debate on the current climate for adding growth externally put to bed the notion that M&A and deal-making are flat, and likely to remain so. New targets are emerging alongside the traditional M&A candidates. Medtronic PLC vice-president of business development and strategy, EMEA, Charity Kufass, cited a number of hot areas in 2019, including moves towards surgical robotics and treatment and care of patients moving out of the traditional hospital setting, including more POC diagnostics.

Digital health is another “really hot” number, she added, but cautioned that there are a lot of ways of interpreting what “digital” means. There is also a trend towards devices for regional markets, i.e. strategies that run alongside the traditional EU- and US- first routes to market. The emerging markets, including China, are getting bigger, so local technologies for local markets might become a trend.

These offer options in a climate where procedure volumes are growing at only 2-3% annually, and price erosion is a fact. Companies like Medtronic are targeting growth in two ways: drive adoption of products; or acquire new technologies and innovations. “We’re not the only ones with good ideas, so those early-stage technologies are something we are looking for continuously,” Kufass said. There is a growing appetite to “go in earlier” when addressing portfolio gaps; its acquisition of the outstanding majority share in Mazor Robotics Ltd., to boost the restorative therapies group, is an example of its moves into novel technologies. “That trend will continue.” (Also see "Medtech Rises To Challenge Of Meeting Infinite Health Care Demand With Finite Resources" - In Vivo, December 2018.)

Very large deals are not top of the menu for Medtronic at present, where the ongoing focus will be a continuation of the policy it has applied since the Covidien acquisition in 2014: driving weighted average growth by acquiring emerging technologies that have faster growth rates.

A lot of big M&A happened in the past five years, but some of it is still a work in progress. “Acquiring is one thing, but integrating is something else,” said Boston Scientific Corp. VP CRM & EP, EMEA, Pierre Chauvineau. The whole activity calls for a commitment to culture change, business transformation, and making deep savings. Some of the recent larger mergers were still working through some of these issues, he noted.

LivaNova PLC’s Matthew Dodds agreed that some of the large deals of the past were still being digested. Some investors did not understand the synergies or the sense of some of them, seeing the expense side rather than the revenue side in a lot of cases, said Dodds, LivaNova’s SVP and head of corporate development. The markets were not impressed on hearing about the rumored Stryker Corp. and Boston merger in fall 2018, but any plan soon evaporated, and Stryker’s share price dipped. But M&A deal numbers overall held up last year – the $100m-plus deals in 2018 were some 30-35, as in the previous year, suggesting that the trend is being maintained.

Chauvineau added that 2019 would see fewer large M&A plays, but “more creative ways of integrating new tech-
nologies from the start-up world.”

Boston made the most recent large M&A play, acquiring BTG PLC for £3.3bn ($4.2bn), and there were noises in certain quarters about the deal being expensive, but Chauvineau’s view is that some of BTG’s technologies can be easily integrated. “Boston has focused on business lines that will allow us to grow in the dynamic markets.” These include structural heart, and atrial fibrillation. “We’re trying to understand which technologies will be winners, and then acquiring them,” he said, pointing to the group’s venture arm which allows it to put money into much earlier stage technologies than in the past. (Also see “Boston Scientific’s Drive To Add To Core Strength Continues With BTG Buy” - In Vivo, November 2018.)

TWO-STEP APPROACH?
The IPO window has been very strong for devices in the past 12 months, and Dodds noted that the banks think the window will stay open and remain strong in 2019. A lot of deals have been dual track – an investment and an option to acquire – but for a while now, the IPO market has offered better valuations.

In terms of early-stage participations, Boston and Medtronic were among the best in this area, said Dodds, but LivaNova has had success too, with mitral valve company Caisson Interventional, and OSA neurostim company ImThera Medical, in particular – both of which were early-stage investments. It becomes harder for LivaNova, a mid-size player, when there is another strategic competing for a technology, and often being the first to the game will be decisive in a bidding war. “I do think that collaborations are going to continue to grow,” Dodds opined.

CRACKING THE DIGITAL CHALLENGE
Minority investments and structured deals are part of Medtronic’s history, but now, looking at how the industry is evolving – and especially with digital applications to devices gaining traction – it is thought that a new approach is warranted. “We don’t have all the capabilities and never will have; we need to move potentially from a closed to an open innovation model,” said Kufass. The question, then, is how does a company do that with someone who may be a competitor? The answers are not yet fully to hand.

The scale of the opportunity is massive, but there are hurdles: the lack of standards and interoperability are both key issues. And even on small projects, getting access to data and generating insights is extremely complex. Then, there is the patient-centric nature of digital solutions, and their application in multiple care settings and via multiple sources of device. All this points to the digital challenge not being conquered in 2019 or even 2020, due to the missing infrastructure and ability to pull it all together. But there is clearly potential.

The challenge for medtechs is that digital requires a different skill set, and it is a completely new business model. The challenge is enormous. Medtronic has worked on pilots, such as partnering with IBM Watson on its diabetes business to try to generate AI and get insights from its pumps. Kufass admitted that “we are not yet really seeing ways of applying it that will really be a game changer for us.”

Chauvineau added that a nice dataset was all very well, but how do you monetize it? Partnerships are the way ahead, he said, also refreshingly upfront about the territory Boston is playing in: “We’re technology companies; we don’t know how to do digital, so we need to find companies that will be partners with us and help big medtech access the segment.” These will usually be young start-ups, as the established players have not been able to deliver all the solutions. “It’s all about the business model and partnering with small companies. That will help find the right value proposition.”

REIMBURSEMENT IS KEY PUZZLE PIECE
Currently, there is a lot of talk in the industry about moving to value-based health care. However, this was a discussion that began 15 or so years ago, Chauvineau noted, and it has still not advanced very far in the medtech world. Systems are not using it and cannot reimburse for it. “The key piece – until and unless we change it – is reimbursement.” There are new types of commissioning being piloted in the EU, but VBHC is still a long way from being the standard for the industry. “But that’s where we need to move to,” said Kufass.

Meanwhile, in the digital health care space, the tech disruptors are circling. It is rightly a concern for the traditional medtech players, but their fears are tempered by the presumption that the big techs will not want to move into medtech. Their play is applying know-how to the pool of data in health care, getting insights and creating a platform that can be monetized.

Where the tech companies will disrupt is in the value that they bring with data, how they analyze and how they bring it back to the consumer. Thus, medtechs will have to partner with them, for these are not the skillsets medtech groups of today have in-house.

The health care delivery models of today are not sustainable. We are at the beginnings of what Peter Fitzgerald last year referred to as the “collision of digital and health care.” At the same time, patients are becoming consumers, and are exhibiting greater willingness to pay to manage their diseases. The big unknown, and an unquantified risk for medtechs, is how much of the value pool the tech disruptors will take. (Also see “Digital And Connected Care Are Pushing On An Open Door – But Is Medtech Ready?” - In Vivo, March 2018.)

ASHLEY YEO

Last year, the biopharma sector raised more than $22bn worldwide in venture capital cash. While US companies led the way, raising $15.7bn in VC rounds, companies in Europe and Asia raised $3.4bn and $3.3bn in private financing, respectively (see page 8).

Considering the sum of VC money being filtered into biopharma firms, Jamie Munroe, global practice leader, portfolio and licensing, at Clarivate, told In Vivo he expected to see “increased levels of deal-making” in 2019. He added that in 2019, oncology would likely remain the most prevalent area for partnering and deal-making. Last year, all of the top-20 oncology licensing deals were in immuno-oncology. “In 2018, we saw more and more discovery-stage oncology deals and I would expect this trend to continue in 2019, fueled by increasing confidence and a lack of promising clinical-stage oncology assets,” Munroe highlighted.

Morten Graugaard Døssing, principal at Novo Seeds, added that the “mega trend” of large pharma in-sourcing innovation to fill pipelines was not likely to fade any time soon. “In this context, there is probably not a direct link between venture financing and subsequent deal-making, but the increased financing will enable venture investors to build more and stronger biotech companies; that will drive increased pharma interest and deal making,” the company told In Vivo.

However, Nick Staples, CEO of UK-based biotech Locate Bio, believes that with more cash available to biotechs, partnering is not as urgent for discovery and early-stage clinical development companies. “Investors are encouraging companies to go it alone, rather than seek early partnering,” he told In Vivo. “It used to be that an early big pharma deal was seen as providing important company validation, but now it is seen as giving a prize asset away too soon. Similarly, early-stage research collaborations that can provide income and long-term value, are increasingly viewed as a distraction to the main game of pipeline advancement,” he said.

Staples joined Locate Bio in November 2018 but was previously chief business officer of Artios Pharma, an oncology R&D company focused on DNA damage response (DDR) technology. Artios raised $85m via a series B financing round in August last year.

He added, “In a lot of the innovative therapy areas, it is the biotechs that have the expertise. The appeal of partnering to access cash is reducing because the investors are putting more money in directly.” Because of this availability of financing, Staples believes the industry will see different collaborative efforts in 2019. “A lot of these innovative therapies need the help of other novel technologies – that’s where companies like Locate come in.”

Døssing commented that while oncology continues to be a hot investment area overall, technologies like DDR and small molecule Protein-Protein Inhibitors (PPIs) are gaining interest. “Immun oncology has been a very attractive area that has resulted in transformational patient benefits. However, there is still a large subset of patients that do not respond adequately to immunotherapies, and thus new treatment approaches that can boost response rate and act in synergy with approved therapies will remain interesting.”

MORE MONEY EARLIER
There was a consensus between Staples and Munroe that the VC well is not likely to run dry anytime soon for biotechs. In 2019, “despite the challenging macro environment,” substantial seed and series A financing was likely to continue, Staples said. “This is an unprecedented time in the industry as we are unlocking human biology and we have new tools. As a result, we have seen VCs all raising new funds, and many have cash to invest,” he noted.

In 2018, vast amounts were raised in early-stage financings by biopharma companies, particularly those in the cancer space. The largest series A of the last 12 months saw San Diego-based Samumed raise $430m for its pipeline focused on regenerative therapies. The company’s pipeline contains several experimental treatments that offer the promise of reversing conditions related to aging, such as osteoarthritis.

After San Diego-based Samumed, the next four biggest series A rounds in 2018 were for companies focused on oncology: Allogene Therapeutics ($300m); BioNTech ($270m); Curon Biopharmaeuticals ($150m); and Tmunity Therapeutics ($135m).

Last year significant amounts were raised by start-up companies. Japan’s Reborna Biosciences Inc. raised $256m, while Boston-based Cerevel Therapeutics launched with $350m in the bank. Cerevel was created in October 2018 by Bain Capital and Pfizer Inc. The company is focused on developing drug candidates to treat disorders of the central nervous system (CNS). Pfizer contributed a portfolio of pre-commercial neuroscience assets to Cerevel, including three clinical-stage compounds and several pre-clinical compounds designed to target a broad range of CNS disorders including Parkinson’s disease, Alzheimer’s disease, epilepsy, schizophrenia and addiction.

ClariVate’s Munroe noted that after oncology, neuroscience remains the next most prevalent therapy area for investors – from both a volume and value perspective.
perspective. And Døssing agreed that "Despite the fluctuating interest from big pharma CNS continues to be attractive given the significant unmet medical needs in the space in general and the lack of treatments providing a real impact on patients’ quality of life."

Meanwhile, Staples highlighted cell and gene therapy as a “hot area” that was likely to see more VC cash in 2019. He added that the industry has already seen unprecedented “mega fund raisings” for cell and gene therapy companies, as well as interesting VC and industry syndicates in this area. For example, in December 2016 BlueRock Therapeutics, a stem cell therapy company based in Toronto, secured $225m in a series A funding from Versant Ventures and Bayer AG. “We are seeing land grabs in this space and people are placing more bets on cell and gene therapies,” he noted.

“While it has been around for more than a decade, it is only now that the technology, regulatory environment, and opportunities for investment and partnering are enabling cell and gene therapies to start delivering,” Staples noted. Locate is developing the technology platforms, TAOS and IntraStem, which aim to address two of the key issues for cell and gene treatments: targeting cell treatments within the body and offering alternatives to viral vectors.

INVESTMENT TRENDS

Locate’s Staples believes the VC market could see a slowdown on immuno-oncology (IO) investments this year. “There has been a lot of ‘let’s see what happens’ when it comes to IO combination enter-
cology (IO) investments this year. “There could see a slowdown on immuno-
thesis coming through for some of the combination treatments that we will know what the next generation really looks like.” Despite this, oncology should still over-shadow other therapy areas in raising significant cash this year, he said.

Craig Wylie, of the consultancy group Arthur D. Little Inc., told In Vivo that two “big categories” in biotech were going to attract VC and private equity (PE) funding in 2019 and 2020. “The first is single genetic mutation products.” He cited Freeline Therapies’ developments in hemophilia as an example. “These are well understood single mutation-based therapies.”

According to Wylie, the second area expected to see increased investment was chronic diseases with more complex genetic and molecular profiles, such as Alzheimer’s disease and multiple sclerosis. Though he noted, investment in these areas was more likely to come from private equity funding.

Wylie also highlighted that precision and personalized medicine would feature in investment trends this year for both the medtech and biopharma sectors – although in different ways. “In medtech look for devices that contain embedded therapeutic AI-type software that understand the therapy and personalize the device to the patient. In biopharma, large patient populations are a thing of the past,” he noted. “Patient populations will be smaller, but targeted and more likely to respond. Look for high response rates in patient trials to indicate well-targeted therapies.”

Evelina Vågesjö, CEO of Ilya Pharma, a small European biotherapeutics company, offered a different perspective. In 2019, she expects to see “more partnering in biopharma for projects where good science is supporting development of next-generation biologics and biotherapeutics... and where the manufacturing and bioprocess challenges can be solved cost-efficiently.” Ilya, based in Sweden, focuses on developing biological drugs for treating wounds in the skin. It, will be seeking private capital this year to progress its technology platform.

Vågesjö added that “big pharma is opening up to more indications beyond their classic therapy areas as their main products go off patent.” She noted that advanced biologics and live biotherapeutic products were starting to get more attention from investors, something she predicted will continue in 2019. As well as the treatment of chronic wounds, Ilya is also exploring indications in the gastrointestinal tract such as irritable bowel disease.
DOES IT GROW ON TREES?
VC FINANCING 2018

LAST YEAR SAW SOME SERIOUS EARLY-STAGE FUNDING, MAJOR LATER STAGE FINANCINGS AND MORE CASH FILTERING INTO SEED ROUNDS. FOLLOW THE TIMELINE OF VENTURE CAPITAL TRANSACTIONS THROUGHOUT 2018 WORTH MORE THAN $100M. A RECORD-BREAKING YEAR FOR BIOTECH FINANCING.

TOTAL RAISED:
GLOBAL TOTAL
$22.8BN

VC GROWTH: 2018 TIMELINE VIEW

BioNTech AG: $270M
Gossamer Bio: $100M
SomaLogic: $200M
Braeburn Pharma: $110M

Rubius Therapeutics: $100M
Oxford Nanopore: $127M
TCR2 Therapeutics: $125M
Hua Medicine: $117.4M

CStone Pharmaceuticals: $260M
Grail Inc: $300M
Brii Biosciences: $260M
JHL Biotech Inc: $160M

January

Kiniksa Pharma: $200M
Moderna Therapeutics: $500M
HeartFlow: $240M
Generation Bio: $100M

February

Allogene Therapeutics: $300M
Constellation Pharma: $100M
Tmunity Therapeutics: $135M
BenevolentAI: $115M
Innovent Biologics: $160M

March

April

May

JUNE

JUNE

ABL Bio: $220M
JHL Biotech: $106M
Stealth Biotherapeutics: $100M
Freeline Therapeutics: $111.76M
Kaleido Biosciences: $101M
Precision BioSciences: $110M
Helix Opco: $200M
I-Mab Biopharma: $220M
DEAL-MAKING: Infographic

**TOP 10 ROUNDS 2018**

1. **JANUARY**
   - BioNTech AG
     - Germany
     - Series A
     - $270M
     - Cancer

2. **FEBRUARY**
   - Moderna Therapeutics
     - MA, US
     - Series G
     - $500M
     - Vaccines

3. **APRIL**
   - Allogene Therapeutics
     - CA, US
     - Series A
     - $300M
     - Cancer

4. **MAY**
   - CStone Pharmaceuticals
     - China
     - Series B
     - $260M
     - Cancer

5. **MAY**
   - Grail Inc
     - CA, US
     - Series C
     - $300M
     - Diagnostics

6. **MAY**
   - Brii Biosciences
     - China
     - ND
     - $260M
     - Infectious Diseases

7. **AUGUST**
   - Samumed
     - CA, US
     - Series A
     - $438M
     - Inflammation

8. **OCTOBER**
   - Cerevel Therapeutics
     - MA, US
     - Seed
     - $350M
     - CNS

9. **DECEMBER**
   - Zymeregen
     - CA, US
     - Series C
     - $400M
     - Biomanufacturing

10. **DECEMBER**
    - Relay Therapeutics
        - MA, US
        - Series C
        - $400M
        - Cancer

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**VC FINANCING**

- **LAST YEAR SAW SOME SERIOUS EARLY STAGE FUNDING, MAJOR LATER STAGE FINANCINGS AND MORE CASH FILTERING INTO SEED ROUNDS.**
- **FOLLOW THE TIMELINE OF VENTURE CAPITAL TRANSACTIONS THROUGH WORTH MORE THAN M A RECORD BREAKING YEAR FOR BIOTECH FINANCING.**

- **TOP ROUNDS**
  - **Compass Therapeutics:** $132M
  - **Ascentage Pharma:** $150M
  - **Gossamer Bio:** $230M
  - **Alector:** $133M
  - **Allogene Therapeutics:** $120M
  - **Atreca:** $125M

- **TOP ROUNDS 2018**
  - **Mirum Pharmaceuticals:** $120M
  - **Roivant Sciences:** $200M
  - **Alphamab Oncology:** $100M
  - **WuXi Nextcode:** $200M
  - **Zymergen:** $400M
  - **Relay Therapeutics:** $400M
  - **Rakuten Aspyrian:** $134M

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**JULY**

- **Samumed:** $438M
- **Tot Biopharm Co.:** $102M
- **Orchard Therapeutics:** $150M
- **Outset Medical:** $132M
- **Tempus Labs:** $110M

**AUGUST**

- **Synthego Corp.:** $110M
- **Cerevel Therapeutics:** $350M

**SEPTEMBER**

- **Zymergen:** $400M
- **Relay Therapeutics:** $400M
- **Rakuten Aspyrian:** $134M
TOP 10 INVESTMENT AREAS

Cancer 141
Diagnostics 56

Drug Discovery 37
CNS 37
Regenerative Medicine 33

Autoimmune/Inflammation 30
Rare Diseases 27
Drug Delivery 18

Infectious Diseases 27
Metabolic 17

TOP 3 ROUNDS

SERIES A
Samumed US Inflammation $438m
Allogene Therapeutics US Cancer $300m
BioNTech AG Germany Cancer $270m

SERIES B
CStone Pharmaceuticals China Cancer $230m
Gossamer Bio US Autoimmune $200m
Helix Opco US Genomics

SERIES C
Zymergen US Biomanufacturing $400m
Relay Therapeutics US Cancer $400m
Grail Inc US Diagnostics $300m

SOURCE: In Vivo | Informa Pharma Intelligence

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Diabetes has been a known problem for over 100 years, and insulin experiments began in 1921, yet the number of diagnosed patients continues to rise. The quality of diagnosis and therapy improves year on year, but Martin Lange asks: how can stakeholders keep treatment costs manageable?

Lange, chief marketing and strategy officer at Ascensia Diabetes Care, believes the solution lies in a combination of technology that suits the user in both how and where it is employed; and a patient-centric approach that seeks to understand patients’ behaviors and motivations while prizing outcomes above all. Basel, Switzerland-headquartered Ascensia has a vision of becoming a “one-stop-shop” for managing diabetes of whatever type and severity. And it is now meeting its self-imposed challenges of moving solidly into continuous glucose monitoring (CGM) and branching out into largely untapped global markets.

That began with its recent global alliance with Zhejiang POCTech Co. Ltd. (POCTech), a Huzhou, China, developer and manufacturer of CGM systems. This major strategic move has seen Ascensia agree to become the exclusive distributor for POCTech in 13 selected markets, and take options over distribution rights in other countries. The group will commercialize a version of POCTech’s current CGM product in these geographies, starting in the second half of 2019. It’s a deal that fits squarely into its expansion strategy.

Deal-making and partnership-building are key strategic planks at Swiss-headquartered Ascensia Diabetes Care, as witnessed by its early 2019 agreement with China’s Zhejiang POCTech.

In a complex marketplace, Ascensia is targeting a move beyond diabetes device technology alone and into disease management, taking into account patient behavioral and psychological elements, as it targets outcomes-based delivery for a wider diabetes population.

So what? With legacy BGM technology and now the solid beginnings in the growing CGM space, Ascensia is aiming for a broader presence in the digital and app-based markets of the future.
renamed Ascensia Diabetes Care (Ascensia was a global product brand name under Bayer). The corporate name might seem new to some, but the group has a legacy of some 70 years in the diabetes space – 1,700 staff, a direct presence in 31 countries, and product sales in over 120 countries. With annual revenues in the region of €1bn ($1.14bn), it is one of the largest stand-alone diabetes companies in the global medtech industry.

Some 10 million patients use Ascensia’s products, more or less on a daily basis. POCTech will change the product mix considerably, but to date, Ascensia’s business model has centered on its Contour portfolio of blood glucose monitoring systems. Speaking to In Vivo, Lange explained the rationale. Blood glucose measurement is the first step toward knowing about a patient’s disease. Over the years, systems for self-monitoring of blood glucose have become more accurate, and where labs are measuring to accuracies of ±5%, Ascensia’s device is achieving an impressive ±8.5%.

Lange’s job since joining Ascensia two years ago has been to take the legacy and set up the company for the future, a broad remit that he says has been “a fun ride” in an increasingly crowded and fast-moving market. BGM is a market that has seen flat growth of late, with reductions in price on standard BGM products, against increasing volumes. This is why Ascensia has been looking to move solidly into interconnected diabetes management and CGM, where it sees future market growth. With POCTech, it now has a CGM partnership, to add to existing business relationships with major diabetes players Medtronic and Insulet. Medtronic is itself a strong player in CGM, having secured US approval in 2017 for its closed-loop artificial pancreas system, the MiniMed 670G.

In BGM, Ascensia’s main rivals are Abbott, LifeScan (acquired from Johnson & Johnson by Platinum Equity in October 2018), and Roche, with its Accu-Chek system. In CGM, besides Medtronic, Abbott is a competitor (including via its new FreeStyle Libre CGM finger-prick free system recalibration device), as is Dexcom (its G6 device is interoperable with other automated insulin dosing systems). Other CGM players include Senseonics Holdings, which has received a US PMA for its implantable Eversense Continuous Glucose Monitoring System (claimed to provide long-term continuous monitoring for up to three months), and Medtrum GmbH, a player in CGM and pumps.

**Ascensia’s Offering**

Ascensia’s platform has been built on developing the market with its legacy of diabetes product development expertise, commercial excellence, and working with the state-of-the-art manufacturing capabilities of its Japanese-based former Panasonic colleagues. “What Ascensia brings to the table is channel access and market access – that is, a global presence and access to patients,” says Lange. Having a global reach is a big advantage, he explains, as it provides the group improved oversight of patient management from a reimbursement point of view. This is useful, given that money flows vary from country to country, and even within countries in some cases.

These twin assets of understanding the market and having production excellence are key strengths. And the group has a narrow focus: “We are only diabetes – it’s part of our mission and vision,” Lange points out. It makes for a clearer path forward, he says, noting that the upside of not being part of a conglomerate is not having to fight for attention, or explain why markets and sales are higher or lower than other divisions are managing.

The R&D effort is channelled through Tokyo and Matsuyama (Shikoku) in Japan, and Valhalla, NY. Japan has more of a corporate R&D function, investing in basic research, whereas the teams in the former Bayer element of Ascensia have been more market-R&D focused, working with the commercial teams, studying patient needs and translating the findings into products.

The partnerships with Medtronic and Insulet fit into the Ascensia rationale, as they are about delivering insulin to the patient. The other part of the process is measuring and diagnostics, where Ascensia excels. “In our Medtronic partnership, our BGM device is used to calibrate the CGM in their closed-loop system. Although there is competition in the diagnostics space with BGM and CGM competing head-to-head, we also see them as complementary technologies,” Lange states.

**China’s POCTech A Cornerstone Moment For Ascensia**

Deal-making and striking partnerships are a key part of Ascensia’s strategy going forward. “We are working on several fronts within the digital space, and identifying partners to work with,” says Lange. Speaking before the POCTech deal was struck, he said that the group is constantly looking at the CGM space, ready to invest in CGM efforts and scanning the landscape there to find suitable partners to work with at various levels. “We are accelerating our foray into CGM with an ongoing in-house CGM program,” he added.

Putting the Zhejiang POCTech deal into context at the 37th Annual J.P. Morgan Healthcare Conference (January 2019), Ascensia’s leadership described it as a cornerstone in the group’s development. There are actually two deals, one on distribution and one on co-development, and together they deliver on the strategy of developing the CGM business via partnerships. That is the view of CEO Michael Kloss, who spoke at the meeting. Under the deal, by the end of 2019, Ascensia will be in a position to have an own-brand product in a selection of markets; and within two to three years it will have a co-developed, marketed CGM product, satisfying short- and mid-term portfolio requirements.

Potential deals are always in the offing, but for now, Ascensia’s focus will be on the POCTech agreement. However, the broader aim of portfolio building does not rule out consideration of other CGM partnerships that can satisfy unmet needs through exciting new technology. “We are definitely looking at other possibilities,” says the group. And on the integrated disease management side, partnerships continue to be investigated in what Ascensia describes as “quite a different space,” which comprises largely a host of small start-ups. But if a third party has better solutions in, say, nutrition or exercise, Ascensia will look to partner with it and draw it into its holistic solutions plans (see below). “We can’t do all of this on our own,” the company readily admits.

**Current Business**

The group’s strongest brand is Contour, which physicians and patients would
know, since 2003, as a high-quality, reliable and easy-to-use BGM product. “We have been consistently gaining share within the BGM space. It’s a market in growth even though prices are eroding, but through our efforts we are gaining share,” Lange says. Volumes are increasing, but sales value is squeezed because of payer pressure. The number of type 2 patients is going up – estimated at 422 million globally (World Health Organization [WHO] 2014 figures), but only one in two is diagnosed.

In the high-frequency tester space, with the introduction of new CGM technologies, usage of CGM systems has been increasing – mainly in mature markets. But reimbursement remains one of the big barriers to adoption of CGM technologies: it is a very expensive product. “We still see in the emerging markets a strong growth in the blood glucose monitoring space, where there remain many undiagnosed patients and access or reimbursement for newer technologies is more difficult,” Lange states.

China, India And Beyond

For instance, in China and India there is low usage of these technologies, so there are clear opportunities there for both BGM and CGM. The latter is growing fast, although it is currently estimated to be used in just 0.5% of diagnosed diabetes patients globally. Thus, it remains employed in a very small proportion of the entire population. But as device sizes and costs decrease, this is a technology that will be increasingly adopted.

There is a very large pool of clients in China and India, and with diagnosis rates going up, they will move more into this space. “We see China and India as key growth markets and we are stepping up our efforts there as well,” says Lange.

Ascensia is increasing the size of its regional sales force teams to support organic growth. In addition, it is looking for partnerships on the BGM side as well as on the digital side with companies in the interconnected diabetes management space. “If we are to commit to China, then we have to invest there, and also for regulatory purposes. Companies that have a local presence have a different regulatory framework to importers,” says Lange, indicating again the strategic nature of China as a business move. “We are actively looking to extend our presence in both of these countries – India and China.”

Besides that, Ascensia’s digital and app technologies associated with Contour offer opportunities in all markets. Lange sees the digital space as exciting because it offers a patient-centric view. “The technology is the easy part,” he says with some irony, adding that the hard bit is: “how to make the lives of our patients easier, better and less cumbersome?”

In this respect, technology is a clear enabler: diabetes is pretty much all about self-management by the patient, who is alone with their disease most of the time. “Technology allows us to understand the impact of dosing and medication, and you can only improve what you can measure,” says Lange. “Good technology is a good tool, but it’s only that – a tool,” he insists. “We need to go further and look at how we can help patients in their day-to-day lives.”

From Technology Company To Disease Management Specialist

This is a big challenge, particularly for type 2 patients – understanding stress, diet, lifestyle and their effect on the disease. Ascensia uses its technology and app to understand and make small improvements to diabetes sufferers’ lives. “In this way, we enable them, and this is part of our broader vision: moving from a device-centric company to becoming a disease management company,” says Lange. Ascensia is evolving from a company that allows patients to understand glucose levels to broaching other risk factors and helping them manage their condition. “That is where we really want to head, and digital is a key part of the solution: it didn’t really exist several years ago.”

All this points to Ascensia moving further into the market and becoming a service provider rather than a technology company alone.

The Value-Based Evolution And Payer Considerations

For some patients, there is medical evidence that, with behavioral change, medication levels can be reduced, or HbA1c levels can be reduced by managing risk factors. “Stating that we aim to reverse that would be setting an aggressive goal. But the challenge remains: how can we help patients to lead better lives? Understanding the disease is a patient-by-patient approach. Our digital solutions seek to make it personal, but scalable,” explains Lange. “It is an environment where patients interact with commercial players to learn about their disease, measure risk factors and key variables, and act on them.”

Talking to payers is another essential part of the remit. Payers look for sustainable improvements within a relatively short time frame, usually 12 to 18 months, in which they can identify proven value. The task of groups like Ascensia is to use data to provide analysis via interconnectivity that keeps the patient at the center. But from a patient’s viewpoint, if he/she is not motivated to engage in certain behaviors, “that’s where it begins and ends.” To forestall such disappointments, Lange says “we need to understand the psychology” of patients. And indeed, over the past 12 months,
Ascensia has been spending much time on human-centric design. This feeds off information such as what a patient does in the morning, evening and night, and where are their pain points.

Diabetes may be a “100-year-old question,” but Ascensia is determined to play a role in advancing treatment and furthering its understanding. That will lead to increased health outcomes, which is what payers are interested in: in fact, defining the value for a payer needs to be crystallized and actively worked toward, Lange stresses. For instance, is it A1c reduction, time in range or other factors? “For this reason, we are working with payers as well as with patients, to understand what is ‘value’ and what people are willing to pay for.”

Getting a common understanding of the question of value is vital – that is, how much will a payer pay, if anything? Medtech is behind pharma in broaching new methods of risk-sharing and pay-for-performance, but that will come in the future, Lange believes. “This industry is not there yet: we are still more pay-for-service rather than pay-for-value-created.” For instance, if a company achieves a surrogate marker, like A1c reduction, there is a common understanding in the industry that it leads to improved outcomes or prevents the onset of certain comorbidities. There is a willingness to pay for that, which is a stepping stone toward the concept of pay-for-value-created.

The group has varying levels of interaction with payers in the US, Canada, France, Germany and the UK. The US is where Ascensia is most advanced, given the country’s pace-setting in digital innovation; and then in France, where there is already reimbursement for telemedicine applications. In all, the group is spending a lot of time in Western Europe and the emerging markets. “We are focused on having a robust and solid solution that demonstrates we are adding value,” says Lange. “That’s the core of everything, and it needs to work.”

**Toward A Holistic View Of Diabetes Management**

The policy at Ascensia is to pursue broader initiatives to develop user-friendly products. Its preferred strategy is to become a one-stop-shop for people with diabetes. Type 1 or advanced type 2 patients are different than patients who have just started on oral anti-diabetes drugs. “Our goal is to identify all their unmet needs from a patient care and personal point of view. What do they need in their day-to-day lives? What are their medical needs? And how can data and services help GPs in their roles – these time-strapped people want to help patients to self-manage, but they often suffer under the weight of data,” says Lange.

Ascensia’s broader view is to find groups of patients where disease management types are common, then focus on diet and/or exercise. Later, it will look at patients’ multiple daily injection regimens and at the challenge of how to keep them in range and dose them accurately.

The task extends to looking at the software and hardware technology enablers that are needed. “That’s where our digital efforts are going, and they are the glue that keeps everything together,” asserts Lange. “Our digital presence is really where our company faces toward the patients and health care professionals. The hardware offers a platform to build data and give us a complete picture of the patient.”

In glucose management, Ascensia is factoring in physical and sleep components, and later will bring the weight component into the equation, to help patients self-manage that element. Then comes the medication information, and with more and more pumps and pens becoming available, the group is studying how it can understand the ways in which all these variables interact and incorporate that knowledge into its mix.

“We do work with other companies – and we want to do that. In digital space, networks have a massive multiplier effect. We can create more value for patients if we interact with other platforms,” says Lange. “There is no wish to reinvent the wheel, but it is important that we help HCPs [health care providers] and patients with the data and analyze it.”

These goals will be achieved via a focus on what Lange sees as the strongest pillars for Ascensia’s business in the future: growing its presence in emerging markets, continuing to invest in CGM and building a digital platform that helps patients manage their disease. At the J.P.
Morgan meeting in January, Ascensia profiled the disease management approach further by announcing its own holistic diabetes management solution, involving coaching and a range of human- and machine-based interactions. This relies not just on BGM, but also on addressing psychological issues, exercise and nutrition. A prototype (unnamed) has been developed, and a trial completed in the US. The next year should see a commercial trial in the US and co-working with commercial payers. “This will road test it in the real world,” Lange says.

Leadership Role
Ascensia pitches itself as a thought leader in the diabetes space, via initiatives such as its Ascensia Diabetes Challenge, a global innovation competition. Through this, the group can start to work with start-ups and up-and-coming companies that are developing innovative solutions based on Ascensia’s criteria in hardware and software. In addition, it uses a panel of HCPs and co-works with external partners. “We also keep close contact with patients and try new things, and we are ‘pivoting’ – moving away from the old school of doing things,” adds Lange. Essentially, Ascensia’s policy means understanding how a person can lead a normal life. This is the big question, and it involves looking at psychological issues. “We need to raise the bar and put much more emphasis on the psychology aspects, and on ways of providing more energy and delivering for them a better lifestyle. That is true human centricity.”

We are focused on having a robust and solid solution that demonstrates we are adding value.

Patient Voice
Reaching out to patients via the blogger community is another channel for Ascensia, as are its networking activities with patient advocacy organizations. The R&D team in Valhalla uses clinical trials to gain feedback on user experience of products.

The overall aim is to make things different. “We need to be able to help patients achieve, one step at a time, sustainable improvement, and this includes factoring in the latest research on behavioral changes,” Lange notes. The other part of this is working with devices to make improvements, for instance in the BGM space, to increase accuracy and improve connectivity. That now extends to CGM as well – making these devices more accurate, easier to use and with longer sensor life, “so that patients actually want to use them.”

Generating the data to lead these activities is a core drive at Ascensia now. Moreover, the market is responding to its efforts. There has been very good early reception of the new Contour Diabetes app, and the overall digital platform that the group is building, Lange claims. Its digital solutions and connectivity are what brings its business offerings – its core BGM business and new commitment to CGM – together. The digital management systems take the data derived from these and other systems – Fitbits, blood pressure cuffs, etc. – and provide holistic diabetes management solutions.

“What you see in the market is a lot of payer receptiveness to work with us,” Lange states. But he knows that, in this crowded and innovative market, Ascensia needs to deliver on its promises in a sustainable way. “We are working on that – and we are working with regulators early on to get their input.” For Lange, this is not a technology company, but a service-oriented, disease management company. “The evolution is underway: it’s about making 1 plus 1 equal 3, and by combining data and making sense of it.”
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Deal-Making Fires Up To Unlock Checkpoint Inhibitors’ Full Potential

Checkpoint inhibitors (CPIs) undo one of the mechanisms that cancers use to evade the immune system. Their success has proven the concept of using the body’s own defences to fight cancer, firing up the far broader field of immuno-oncology. But checkpoint inhibitors are reaching an impasse. It is now understood that they are effective only in the minority of tumors which already show a low level immune response. This is most likely to be the case in melanomas for example, with high numbers of gene mutations and thus multiple neo-antigens. Many more tumors are immunologically ‘cold’ – they have relatively fewer gene mutations and are therefore completely silent to the immune system, and to the effects of CPIs.

Combining CPIs with other tools that trigger an underlying immune response may vastly expand their efficacy and reach. Hence the scramble to develop those technologies, driving oncology’s dominance of the outsized 2018 IPO and financings roster. Over a third of IPO funds last year went to cancer companies, according to Strategic Transactions. And there were more than three times as many oncology-focused alliances than in any other therapy area (except neurology, where deal numbers were outpaced just 30%). (Also see “2018’s Top Biopharma Deal-makers” - In Vivo, January 2019.)

Industry’s development pipeline saw an almost 70% increase in the number of immuno-oncology candidates between September 2017 and September 2018, according to New York-based Cancer Research Institute.

Many things can stimulate the immune system; the challenge is finding the most effective, targeted and least toxic options. Cancer vaccines and oncolytic viruses are two increasingly prominent classes of co-administered immune-system stimulators. Therapeutic cancer vaccines use cancer-specific antigens to activate and direct the immune system. Merck & Co.’s Keytruda is already elbowing its way into the top ten best-selling drugs. But it, and its expanding cohort of competitors, could be much bigger. Companies and investors are scrambling to identify the technologies that can unlock checkpoint inhibitors’ potential in the 70% or more of tumors where they do not currently work. That activity is reflected across 2018’s licensing deals, M&A and financings.

BY MELANIE SENIOR

Combining checkpoint inhibitors with other tools that turn on the immune system may vastly expand their efficacy and reach.

Last year, three oncolytic virus companies were snapped up by pharmaceutical firms seeking to expand their immuno-oncology (IO) portfolios and secure a lead or foothold in the checkpoint space.

So what? Oncology-focused investors and pharmaceutical companies are balancing risk across a broad portfolio of IO approaches and modalities. Deal-making activity in the IO space around novel approaches and combination options shows no sign of abating yet.
Oncolytic viruses are designed to trigger an immune response and to directly attack cancer cells as well (they can also be programmed to carry additional payloads). There are marketed drugs across both categories: Dendreon’s Provenge (sipuleucel-T) extracts patients’ white blood cells and programs some of them to provoke an immune reaction against prostate cancer, after re-injection. Amgen’s Imlygic (talimogene laherparepvec; T-Vec) uses a modified herpes simplex virus to attack advanced melanomas and deliver an immune-stimulatory molecule, human granulocyte macrophage colony-stimulating factor (GM-CSF).

Neither Provenge nor Imlygic has shone as a standalone therapy. (Amgen does not single out Imlygic sales, but reported figures suggest about $60m per quarter). But scientists now understand that the potential of these drugs is in partnership. Hence both cancer vaccines and oncolytic viruses – themselves encompassing a wide range of approaches and technologies – have attracted significant deals and financings over the last 12-18 months.

In 2018, three oncolytic virus companies were snapped up by pharmaceutical firms seeking to expand their IO portfolios and secure a lead or foothold in the CPI space (see Exhibit 1). Merck bought Australia’s Viralytics in February 2018 for $400m. Johnson & Johnson embraced Benevir in May, and Boehringer-Ingelheim acquired Austria’s ViraTherapeutics in September. No pharma is relying exclusively on OVs, but a growing number want one in the bag – including those with a later-to-arrive checkpoint inhibitor. “There are six checkpoint inhibitors battling it out. Keytruda and [Bristol-Myers Squibb’s] Opdivo (nivolumab) are looking at how to preserve and grow their [leading] positions. The other four are trying to find white space. They need something to attach to – and that’s where oncolytic viruses will play a critical role,” said Andrew de Guttadauro, head of business development for oncolytic virus player Oncolytics, which is running for a deal of its own in the second half of 2019.

Oncolytics’ vision, like that of recently-listed Replimune, is to develop a ‘universal’ oncolytic virus that is suitable for use with multiple checkpoint inhibitors.

Oncolytics’ lead asset pelareorep, a reovirus, is currently in investigator-led trials with Keytruda in pancreatic cancer, with Opdivo in multiple myeloma, and in a company-funded breast cancer study with Roche’s Tecentriq (atezolizumab). Replimune’s Phase I/II candidate RP1, a modified herpes simplex virus (like Imlygic), is in trials with Opdivo for solid tumors and will soon begin a study with Regeneron/Sanofi’s sixth-to-market Libtayo (cemiplimab). (Replimune is a re-incarnation of UK company BioVex, acquired in 2011 by Amgen for what would become Imlygic.)

Oncolytic viruses are all quite different from one another, though. So it is unlikely that any single candidate emerges as ideal. There are multiple different virus types, which naturally differ in size, and architecture, host cell entry mechanism, replication speed and location, and how they interact with the immune system. And that is before any genetic modifications or additions, such as those designed to add immunogenicity, selectivity, or cytotoxicity. As such, “there is a lot more difference between two types of oncolytic virus than between, say, [checkpoint inhibitors] nivolumab and pembrolizumab,” explained Dmitriy Zamarin, medical oncologist at Memorial Sloan Kettering Cancer Center. The huge range of oncolytic viruses in development reflects this heterogeneity. Some are RNA-based, others DNA-based; some are extensively engineered, others are not. Many are delivered intra-tumorally; a few, like PsiOxus Therapeutics’ enadenotucirev are given systemically. (Enadenotucirev is in a Phase I trial with BMS’ Opdivo; early evidence suggests it may work in both primary and metastatic tumors). Each is likely to be suited to different tumor-types or settings.

That means there is room for multiple different combinations – and more deals. Indeed, potential partners for oncolytic virus development candidates “have a much more nuanced perspective on the class than even just two years ago,” said Oncolytics’ Guttadauro. “They used to think one oncolytic virus was as good as the next.” Oncolytics may particularly welcome these evolving views. The company in 2014 released unconvincing data from a combination study in head and neck cancer of pelareorep with chemotherapeutic drugs. Since the arrival of checkpoint inhibitors, and with accumulating clinical data, more is understood about the strengths and weakness of different oncolytic virus approaches – and where each may fit into an increasingly complex treatment armamentarium. (Oncolytics is hoping that the Tecentriq combination data, due in the third quarter, may generate some deal-making action. The company already has a 2017 deal with China’s Adlai Nortye to market the virus in the Far East.)

Despite their many differences, oncolytic viruses all have the same fundamental, and highly challenging, balance to strike: between anti-viral and anti-tumor immunity. Our immune systems have
evolved to eliminate viruses, rather than let them enter and fire up that same immune system against cancer. Oncolytic virus design must, somehow, allow both evasion and stimulation.

Merck’s leadership in the checkpoint inhibitor space means it has most to lose by not securing the winning partners. It has hundreds of Keytruda combination studies ongoing, with a variety of agents. A Phase III trial of Keytruda and Amgen’s Imligic in melanoma is particularly eagerly-awaited by the oncolytic virus community. The 700-patient, fully recruited MASTERKEY-265 study was due to report before the end of 2018. But the trial is event-driven, with overall survival as a key primary endpoint – meaning the delay is good news. Earlier data from the same combination has hinted at a doubling of objective response rates.

Similarly, strong data from MASTERKEY-265 (also known as KEYNOTE 034) will help prove the concept of using oncolytic viruses to turbo-charge checkpoint inhibitors, perhaps triggering another round of licensing deals or acquisitions.

Already, Merck has other virus-linked shots on goal with Keytruda, including DNATrix’s adenovirus-based tasadenoturev (in a Phase II combination trial for glioblastoma) and TurnStone Biologics’ MG1-MAGE3, an OV/cancer vaccine hybrid approach based on the Maraba virus (in a Phase I/II for non-small cell lung cancer). The Viralytics acquisition brings it Cavatak, another RNA-based virus in multiple trials with checkpoint inhibitors – including a Phase I study with Keytruda in NSCLC and bladder cancer. “Oncolytic viruses do lots of things when injected into a tumor; it’s a really multi-faceted approach to increasing the immune micro-environment in a way that allows drug like Keytruda to come in and help,” said Merck’s VP, global clinical oncology, Eric Rubin. In the Keytruda combination trial, Cavatak is administered systemically, rather than intra-tumorally, as for Imligic and several other development-stage oncolytic viruses. Systemic delivery ensures a widespread effect – but may mean less potency within a given lesion. Rubin said he was particularly interested in the systemic route given its convenience and its potential to expand Keytruda’s reach beyond the most accessible lesions.

Potential partners for oncolytic virus candidates are not limited to companies with a marketed checkpoint inhibitor. Those with development-stage candidates have an even more urgent need for differentiation. One way to do that is to get to market as part of a ready-made combination with a virus, shown to amplify tumor-killing in certain settings. For oncolytic virus players, “that means enticing partners, early on, and generating data together,” said Jan Adams, managing director at EMBL Ventures.

An example: Boehringer Ingelheim’s 2018 acquisition of preclinical ViraTherapeutics (in which EMBL was a lead investor). Boehringer’s own checkpoint inhibitor is still in Phase I, but it had been working with ViraTherapeutics since 2016. Like other companies vying for position in the red-hot immuno-oncology space, Boehringer wants to leap-frog the competition with next-generation candidates and combinations. In April 2018 it licensed from France’s OSE Immunotherapeutics a pre-clinical checkpoint inhibitor that works very differently from those on the market, harnessing a different kind of immune cell.

Johnson & Johnson, which bought preclinical BeneVir, does not have a late development-stage checkpoint inhibitor. Nor does AbbVie, which in October 2017 signed an option to access up to three of Turnstone Biologics’ oncolytic viruses, including its Phase I/II lead candidate. “Very sophisticated companies without [advanced-stage] checkpoint inhibitors of their own are investing; they understand that [in order to compete in oncology] they need a play in oncolytic viruses,” noted Ted Ashburn, CEO of preclinical OV player Oncorus, whose investors include Celgene and Astellas (Celgene invested before its proposed acquisition by BMS).
Vaccines’ Second Coming

Cancer vaccines provide another useful means of mobilizing the immune system to complement and enhance checkpoint inhibitors. Indeed, the distinction between cancer vaccines and oncolytic viruses is blurry: both use antigens to light up the immune system. Cancer vaccines pick out and present a specific antigen, sometimes personalised to an individual’s cancer. Oncolytic viruses throw a range of antigens, including viral antigens, at the tumor.

Cancer vaccines have, until now, largely disappointed. Scientists did not understand enough about the immune system, nor did they have the right tools to find and select the most appropriate antigens. Improvements on both fronts have resurrected the field. There were at least four cancer vaccine IPOs in 2018, including the largest in biotech’s history, Moderna Therapeutics’ $600m haul (see Exhibit 2) Granted, that company’s broad messenger RNA-based platform includes a range of immuno-oncology approaches alongside cancer vaccines. But it was not alone. Gritstone Therapeutics and Neon Therapeutics both pulled in close to $100m. Pre-and post-IPO funding was healthy in 2018, too. Advaxis, whose Phase III cervical cancer vaccine candidate, axalimogene filolisbac, uses attenuated bacteria to deliver antigens, generated almost $40m from two follow-up public offerings. Genocea pulled in $51.7m in January, and Moderna presaged its IPO with close to $700m of private funding. Germany’s BioNTech (working with mRNA and a host of other modalities) generated a whopping $270m series A in January 2018.

Selecting the right antigens – cancer-specific proteins that wave a red flag at the immune system – is critical to cancer vaccines’ effectiveness. The technology or approach used to do so is what differentiates many cancer vaccine start-ups.

Cancer is notoriously good at evading the immune system – hence the rationale for checkpoint inhibitors. Cancer emerges from our own, healthy cells, and can cloak itself in molecules that look relatively normal to our natural defences, hiding the abnormal players deep inside tumors. Scientists now have better tools for picking out some of the most foreign-looking antigens – those that only highly-mutated tumor cell genes might generate, and which are otherwise entirely absent from the human genome. Such ‘neo-antigens’ may be particularly adept at eliciting a potent immune response, if they can be suitably exposed. Most of these neo-antigens are unique to individual patients’ tumors, meaning a highly personalised treatment approach.

Many new cancer vaccine companies use computer algorithms to predict which of the many hundreds of thousands of potential tumor mutations will generate the most potent, immunogenic antigens. For instance, Neon Therapeutics’ bioinformatics engine, RECON, uses deep learning informed by large data sets (including, but not limited to, DNA and RNA sequences from tumor and normal tissue). Its lead neo-antigen-based vaccine is in a Phase I trial with BMS’ Opdivo, in melanoma, bladder cancer and NSCLC.

Gritstone’s artificial intelligence (AI)-based EDGE platform is also trained on extensive human tumor sample data. EDGE predicts which neo-antigens will be presented on the cancer cell surface; candidates are then delivered using a prime-boost regimen (like some conventional prophylactic vaccines) to further optimise the cancer-targeted immune response. The system is primed using an adenovirus-based vector to trigger an initial T-cell response; that response is then boosted with an RNA-based vector. Both contain the neo-antigen. The approach is shown in preclinical studies to generate a significant antigen-specific T-cell response.

The company’s lead personalized vaccine program features in a Phase I/II study in combination with CPIs across a range of solid tumors. BMS signed up in July 2018 to test the personalized approach alongside both Opdivo and fellow CPI Yervoy (ipilimumab).

The team at Cambridge, MA-based Genocea claims its approach to finding suitable neo-antigens trumps its rivals’ in silico efforts. Genocea uses in vitro biological assays to determine which tumor neo-antigens actually trigger T-cell activity – rather than relying on computer-powered predictions, many of which “thus far don’t seem to be that good,” claimed Genocea CEO Chip Clark. “Biology is too complex to use algorithms to identify the best T-cell target,” he continued. Our highly intricate (and still only poorly understood) immune responses may even include inhibitory neo-antigens that actively suppress anti-tumor responses, Clark surmised, citing early animal work at the company.

The jury’s still out on Genocea’s technology (and on those of most of its competitors): the lead neo-antigen-based vaccine has just begun the first stage of a Phase I/II trial assessing safety and immunogenicity in treated cancer patients who no longer show evidence of disease. Those immunogenicity data are expected in mid-2019. Efficacy and safety in combination with an approved CPI will be assessed in a second stage of the trial.

Meanwhile, Genocea hopes that its focus on the “fundamental” question of whether there is a T-cell response to a given antigen – regardless of what modality is chosen to present that antigen – positions it strongly for further deal-making in 2019. “The temperature remains very warm [for deals in IO]. I think deals will be done, and hope that Genocea will be an active participant,” said Clark.

Moderna is not relying only on bioinformatics for antigen selection, either. And its technology platform may give it a little more leeway around precisely which antigens to select for optimal effect. It uses messenger RNA – a molecule that carries genetic information from DNA to protein-making machinery – to deliver cancer-related antigens to patients. mRNA only delivers the code for making the antigen, not the antigen itself (or epitope – the part of the antigen that immune cells actually recognise). That allows the company to insert code for several epitopes, and “let the cell’s machinery figure out what is most likely to bind” with the molecules used to present antigens to the immune system, explained Moderna’s chief medical officer Tal Zaks. “We don’t have to single out the right epitope.” Nature can take care of that.

Moderna’s mRNA platform first attracted partner Merck in 2015, around an infectious disease vaccine. The companies have partnered several times since in oncology. In 2016, the big pharma took an interest in Moderna’s lead personalised cancer vaccine, which will soon begin...
a Phase II trial pitting it plus Keytruda, against Keytruda alone. A second vaccine candidate contains mRNA for KRAS, an oncogene found across several epithelial cancers (including lung, colorectal and pancreatic). Merck signed up to this in May 2018 and will soon initiate a Phase I trial, both as monotherapy and with Keytruda. Merck may opt-in on a 50/50 global net profits and cost share once human proof-of-concept is achieved.

**Efficacy Vs. Practicality**
Creating a vaccine that can be used across more than one individual may prove key to commercial success in the space. Prior efforts to prime the immune system focused on such shared tumor-associated antigens; the problem was that some of these are found on normal cells, too. Advaxis’ approach with axalimogene filolisbac uses an oncoprotein found in all human papilloma virus (HPV)-associated cancers, giving this treatment a potentially wider reach. The program has made it into late-stage trials, but it is not yet at the finish line: the FDA in January 2019 put the Phase III trial in HPV-associated advanced cervical cancer on clinical hold, albeit for CMC reasons rather than safety.

The shift toward neo-antigens that are unique to particular patients’ tumors may mean better efficacy (and perhaps a lower chance of off-target effects). But they will also be difficult and expensive to scale-up. Manufacturing and administration hurdles have limited the uptake of personalized adoptive T-cell therapies like Gilead Sciences’ Yescarta (axicabtagene ciloleucel) and Novartis’ Kymriah (tisagenlecleucel).

Hence most neo-antigen-focused cancer vaccine companies are also investigating off-the-shelf variations. Gritstone and Neon have preclinical programs using a fixed set of neo-antigens that are shared across a wider sub-set of cancer patients; Genocea also has discovery work ongoing on a shared antigen vaccine. Turnstone’s non-personalized approach combines both oncolytic virus and cancer vaccine in one treatment. The 2-in-1 therapy is administered systemically using a two-step prime-boost regimen. MG1-MAGEA3 comprises an engineered RNA-based Maraba virus expressing tumor-associated antigen 3 (MAGE 3), which is prevalent on many solid tumors. Priming uses a non-replicating adenovirus encoding the same MAGEA3 antigen. The Maraba virus boost follows two weeks later, accelerating the immune response to the cancer, including at metastatic sites, and unleashing other modes of attack characteristic of OVs. MG1-MAGEA3 is currently in a Phase I/II trial alongside Keytruda in non-small cell lung cancer. (There’s still room for a checkpoint inhibitor to help the T-cell army along, preventing exhaustion as the tumor micro-environment heats up.) AbbVie has first dibs on this, and two other earlier-stage candidates.

Turnstone’s team also had manufacturability in mind when selecting its virus. The Maraba virus, isolated from Brazilian sandflies, does not require cell lysis to be harvested: it just buds off from the cell. Turnstone’s virus-cum-vaccine was also relatively easy to administer, according to Mike Burgess, president of R&D. “It is infused [systemically] over an hour and the majority of patients go home within six hours,” he said. “That’s important for cancer patients.”

Several other oncolytic virus developers also point out that their candidates are easier and cheaper to make and administer than the current generation of chimeric antigen receptor-based T-cells.

**More Cost-Effective Followers?**
As investment dollars pour into IO, tools and platforms are evolving rapidly, producing a plethora of next-generation oncolytic virus and cancer vaccine technologies and combinations. These are not only about more effective, targeted immune-system activation and cancer-killing. The challenging reimbursement environment means that for many, practical considerations such as cost and access are front of mind too.

Oncorus is working on a ‘synthetic’ oncolytic virus, whereby genetic material encoding the entire oncolytic virus is hidden within a lipid nano-particle that’s injected directly into the tumor. This produces replication-competent viruses in situ, bypassing the challenge of evading viral immunity. It may also mean lower costs, since such a synthetic virus could potentially be made with simple, cheap components, in a convenient, accessible manner.

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**Oncolytic viruses do lots of things when injected into a tumor; it’s a multi-faceted approach to increasing the immune micro-environment.**

– Eric Rubin

Merck
DEAL-MAKING: Coming Up In Oncology

and affordable formulation, suggested Mitchell Finer, Oncorus’ founder and executive partner at investment group MPM Capital.

Transgene, Replimune and others are programming oncolytic viruses to not only unleash immune-stimulatory signals and lyse cancer cells, but also to locally produce other cancer drugs – including CPIs. Beyond the convenience of such an all-in-one therapeutic bundle, this approach may also, one day, prove far more cost-effective than combining multiple standalone therapies.

There Are Still Unknowns ...

Yet Finer and other leading scientists in the field are quick to admit that there is a long way to go – notwithstanding the excitement (and data) building rapidly around the space. The concept of combining oncolytic viruses with CPIs may be strongly supported by early clinical work, but it still lacks validation from a definitive, late-stage clinical trial. Dosing and administration need to be figured out, both for viruses and vaccines. So does the optimal checkpoint inhibitor-virus or vaccine combination for any given cancer type or setting.

The variables are considerable – and will increase. There are many other IO approaches beyond oncolytic viruses and vaccines. They include CAR-T cell therapies and other adoptive cell therapies, bi-specific antibodies and other kinds of molecule targeting precise cell components or immune-system actors – plus a next-generation of checkpoint inhibitors targeting different molecular pathways.

The relative strengths of, and best applications for, the multiple modalities and targets across the burgeoning IO field have yet to be determined. These uncertainties help explain volatile stock prices. Moderna, for all its popularity with private and public investors in 2018, has lost a third of its stock value since its IPO. Gritstone has also had a bumpy ride. They also explain why oncology-focused investors and pharmaceutical companies are balancing risk across a broad portfolio of IO approaches and modalities.

“We don’t know which [technologies] will work. We have tools that we think will apply to different diseases. But [figuring out which] will not be easy, and won’t happen overnight,” warned MPM’s Finer.

... But The Deals Continue

Meanwhile, IO deals show little sign of abating. Sanofi in January 2019 agreed to co-develop an mRNA-based cancer immunotherapy with Germany’s BioNTech, extending the partners’ 2015 collaboration. BioNTech already has a half dozen other partners, including Roche’s Genentech, which is collaborating on the biotech’s lead personalised RNA-based cancer vaccine, which completed Phase I trials in melanoma. Private BioNTech, supported since 2018 by institutional as well as family office investors, wants to hold onto some of its assets in order to build a global business of its own. But “if we can get to market quicker with a partner, then we might,” said Sean Marett, chief business officer and chief commercial officer. Marett is not ruling out further deals, as long as they bring complementary strengths; nor is he ruling out a public listing, if that proves the most appropriate financing path. (Indeed, Bloomberg in early February reported that the company was considering a US IPO.) “It’s about creating options,” Marett added.

Celgene continues to deal even as it loses its independence to BMS. In mid-January 2019 it bought an option to Obsidian’s CAR-T cell therapy-enhancing technology, which modulates the activity of two key immune-system players, IL-12 and CD40L. It also paid $80m upfront and took a stake in one-year-old, Boston-based Kyn Therapeutics, whose early programs target molecules thought to be involved in tumors’ immune-system protection mechanisms. These may provide yet another means of turbo-charging CPIs. The IO dealmaking frenzy looks set to continue through 2019 - and perhaps beyond.

Comments:
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As China Looms, Sofinnova Partners Keeps The Faith In A Resilient Europe

In this first installment of VC Playbook, a new series profiling venture capital groups in biopharma and medtech, In Vivo talks to Antoine Papiernik, managing partner and chair of Sofinnova Partners – Europe’s largest and oldest VC devoted to the life sciences, with €2bn under management.

BY WILLIAM LOONEY

Papiernik has a simple and jargon-free criteria for investment at Sofinnova Partners: identify an unmet medical need and address it with differentiating technology that appeals to patients.

As part of its global growth plan, Sofinnova (founded 1972) is looking away from traditional drugs and devices to industrial biotech.

So what? Europe needs to work harder to remain competitive in a global life sciences capital market soon to be dominated by a duopoly consisting of the US and China. Current government support is helpful but not sufficient

In Vivo: Venture capital is a high-risk world with no visible rule book to determine how, when and where to invest – the options are legion, particularly given the new disruptive technologies that are transforming the business model for life sciences. Innovation can emerge from anywhere, as evidenced by the fact that a fellow Frenchman, Georges Doriot, founded the world’s first publicly listed VC, American Research and Development Inc., way back at the end of World War II. How did you enter the VC space? What skills and character traits have been instrumental to your advancement – and is your own circuitous career path still viable in the hyper-competitive VC climate of today?

Antoine Papiernik, managing partner and chair, Sofinnova Partners: My move to life sciences investing was more serendipitous than deliberate. I was educated in France and took my first job at Unilever, in their UK retail health and beauty business, where I learned the importance of looking beyond the product to understand what drives consumer behavior. After time out for an MBA at the University of Pennsylvania’s Wharton School, I took a position in the Czech Republic for the two-century-old French public institution, Caisse des Dépôts et Consignations [CDC], to work on its private-equity strategy in central and eastern Europe. In 1995, the CDC decided to create a large VC fund investing in IT and life sciences, and offered me the great opportunity to join it at the start. I opted for the life sciences side, for no other reason than both my parents were physicians; my father was an obstetrician and my mother practiced immunology. I knew nothing about the life sciences but I quickly became engaged to the point that I decided to make it a focus of my career. When I was offered a partner position at Sofinnova Partners, which even then was Europe’s leading VC in health and life sciences, as it is now, it was difficult to refuse. I joined in 1997, helped to grow the
practice in pharma, biotech and medical devices, and now 22 years later I am one of the managing partners and also serve as chair of the firm.

As far as getting into the business, what I was able to do two decades ago is virtually impossible today. The complexity of the pharmaceutical and medical devices sector demands that a young associate should have an advanced degree in medicine or science – without it, you won’t be recruited. The exception might be for a candidate with a track record in investing, but it’s the kind of experience you don’t get outside our circle. What amuses me about this trend to credentialing is that being a good scientist is no guarantee of success in VC investing. I’ve learned at Sofinnova that success depends not just on a command of facts but more on people skills. You can have the best data and technical expertise but still lose a deal if the principals can’t negotiate or don’t get along. There are a lot of brick walls in the VC business. Dismantling them takes a good understanding of human nature and you can’t learn that from a textbook.

A Better Place

Is it easier to do business in Europe today than when you began investing in life sciences? Is the region becoming more open to the concept of risk and entrepreneurship as it is practiced in the US?

Europe has changed in the past two decades. It takes time to move away from a historic, culturally reinforced mentality that risk is bad and failure never allows for a fresh start. It has been said that there are two things we French dislike in equal measure: failure and success. But the momentum of change is unmistakable. There are some creative outlets for financing, and capital is more readily available to secure the designs of a budding class of entrepreneurs, whose ambitions had to be drip fed for years due to a shortage of seed funds. The situation is not ideal, but today we are several magnitudes higher in terms of the ability of businesses with good ideas to raise cash when they need it.

Looking forward, the key question is whether Europe can keep up the pace against the talent and resources of a $3 trillion market for health care in the US as well as the massive scientific scale-ups now taking place with government support in China. Increasingly, Europe’s fortunes are intertwined with a global, highly mobile – and often volatile – network for capital investment. The competition – for cash, for new science, for human capital – is coming with an intensity we have not experienced before. Nevertheless, I think that the pressure from a global marketplace is good for Europe. It concentrates the mind. But I temper that by stating I’ve always been an optimist at heart.

Yes, but why have there been so few European VC success stories that stand out in comparison to the deep reservoir of marquee investments we have seen in the US? Can you point to any of note in European biopharma?

The US casts a long shadow; it’s no surprise that Europe looks a bit pallid in comparison. Europe came to this space three decades behind the US, which had some early successes like Genentech Inc. and Biogen Inc. that remain precedents for the entire industry today. Europe has had time to catch up – recall the adage that you must know how to walk before you run. I was associated with the initial funding round of the Swiss drugmaker Actelion Pharmaceuticals Ltd., which was acquired in 2017 by Johnson & Johnson, for $30bn – the biggest success story for biotech in Europe to date. Other such profitable deals are still to come. I’d point out as well that when I began working in life sciences investing in 1997, there was not a single biotech company with a market capitalization above $1bn based in Europe. Today, there are 20. Development of any new industrial sector is slow; you might say that Europe is the adolescent in a room of mature adults.

How To Get Noticed: Aim High And Speak Out

You serve as a member of the board for many emerging pharma and biotech companies based in Europe. What are the opportunities and challenges in playing in this space? What have you learned about corporate governance in the European context?

My exposures are highly diverse. I sit on the boards of European companies that
filed to go public on the local Euronext stock exchange and stayed put. I am also on the boards of companies based in Europe that opted to list at the much higher profile NASDAQ exchange based in the US. I’ve been involved in virtually every option a European company can pursue in registering and raising money on the public and private market. The decision on what path to take is not an easy one – this is why we in Europe have a lot to do in making the process work better and fulfilling the promise of our rich base in the innovative life sciences. If you are a European company that goes public in Europe and does well, you still won’t garner much attention from the major US investment giants like Fidelity, Wellington Management or Janus. All of them are very US-centric, and understandably so. But that emerging Dutch biopharma that opted to list on NASDAQ faces the same predicament: in a caucus of giants, you’re too small to be a priority to these investors as either a growth opportunity or a hedge against a market downturn on Wall Street.

My point is European capital markets are still not scaled to the raw commercial potential that exists in the region. Company boards must be versatile and opportunistic to overcome the disadvantages of being in a secondary, under-resourced market. What we wish for is a world where the Fidelity fund manager with a $20bn portfolio will be agnostic about our geographic base and instead focus on our business plans, our management and our cash flow. There shouldn’t be any difference whether a company is based in Boston, San Francisco – or Timbuktu. But that’s magical thinking for now.

Thus, the task for Europe is to improve on the infrastructure necessary to build connections between the public market and specialist investors willing to think long term. It begins with accepting the hard truth that there is only one NASDAQ, and it’s not based in Paris. A local competitor, EASDAQ, was founded in Paris in the 1990s to emulate the NASDAQ model but it failed quickly. Today, while the Euronext exchange is an important sign of progress, it cannot deliver the $200m or $300m a promising biotech firm needs to progress to that next phase of growth, which usually requires a multiple of five or more over what was raised through the IPO. I am not ready to wait two more decades for this to happen, so the only viable recourse for the near term is to find ways to work around NASDAQ and to meet the strict liquidity requirements it expects from its members. In other words, European start-ups in life sciences need to raise the bar and go for the money where it is. I know the government industrial policy folks in Europe don’t like to hear this message, but I am an investor, not a politician.

How has Sofinnova managed to thrive in this promising but still constricted environment for growth? Describe the investment philosophy – and does Sofinnova define itself as a European or global player in VC?

From a purely geographic perspective, 75% of what we do takes place in Europe, which we continue to define as inclusive of the UK. Our principal local markets are the UK, France, Germany, Scandinavia, Switzerland and the Netherlands. We see the UK continuing as a viable business opportunity for us, regardless of the outcome of Brexit. The remaining 25% of the business centers on the US, though we are slowly building an understanding of Asia, mainly Japan and China. On a sectoral basis, 75% is in big pharma and biotech and 25% in medtech.

In summary, I’d say our focus is on biotech and the opportunities for it that exist in Europe. That said, Sofinnova today has a much more diversified orientation than when I joined the firm in 1997. Back then, we were almost entirely French. If you go now to our website, you will see native French-speakers are a minority. We are also characterized by our gender diversity, which is exceptional in comparison to the norm both here in Europe and in the US. We employ men and women from dozens of geographies because it’s good for our business model. There is a real local culture of investing and thus we want people who can give us an edge by intuitively knowing what it takes to win a deal in Italy compared with winning the business in Denmark or the Netherlands.

Impact Investing Comes Of Age

Where do you focus your resources – what’s the preferred investment stage and scale?

Our reputation is rooted in making strong bets on companies with differentiating technology, supplying seed financing in return for an early-stage stake in the business. Since 1989, we’ve managed eight consecutive capital funds, all geared to finding start-ups to mid-size companies with a future linked to a promising technology but who lack the funds to turn their ideas into products. Last year, we introduced a late-stage crossover fund focused on late-stage private or listed businesses capable of progressing to fully integrated companies able to compete in important areas of unmet medical need. Our investment is geared to positioning these companies so they can raise their market cap from a few hundred million to the billion-dollar range – the minimal size required to survive on a larger field with competitors outside Europe.

Interest in this pathway is also growing in the US, as evidenced by the merger agreed in November 2018 between the world’s largest private equity investor, Blackstone Group LP, and the VC firm Clarus Ventures Inc. to form Blackstone Life Sciences with a goal to expand funding for growth-stage investments designed to propel the advance of breakthrough products for unmet medical needs.

We are not alone in seizing the potential in this space. All of us in VC see it as much more than filling a gap: it’s actually like fitting the pieces in a puzzle because you are eager to see what the picture looks like in the end. In our case, it’s a new platform, product or technology that helps patients who previously had no other options. We love to see start-ups where a bet of €750,000 eventually produces a company with revenues in the hundreds of millions of euros. And when that company reaches the billion-euro market capitalization we can say we’ve been proactive – consequential – at every stage of the life sciences value chain. That’s what fulfills our mission as an investor who literally shapes the future.

Can you identify some of your most successful investments? Alternatively, are there any deals that proved to be a setback for you?
In 22 years, it’s fair to say I’ve had a mix of both. I can readily cite two very recent examples that showcase the merits of a value-based approach to investing. When you can raise capital that empowers an outstanding management team and brings safely to market a product that saves patient lives, there is no better place to be. I mentioned Actelion, where I made our first investment in the Series A note, in April 1998. We stayed with the company in the formative years, until a few years after the IPO. We were not shareholders by the time Actelion sold itself to J&J’s Janssen Pharmaceutical unit early last year. But the overall return to Sofinnova from this early investment proved to be a double-digit multiple; and the number didn’t start with a one or a two. But there was also the societal impact that figures just as high in my mind, expressed by the many patients who told us how Actelion’s leadership in therapies for rare diseases helped save their lives.

Another example is the chance we took as sole investor in a private medtech company, ReCor Medical, which developed a renal denervation device that lowers blood pressure in patients with severe hypertension – one of the world’s biggest killers. We experienced some ups and downs but the management team stayed the course, with an excellent peer-review study published in The Lancet that finally opened people’s eyes to the promise of this new device. In July 2018, we relinquished our independence and sold ReCor to Otsuka Pharmaceutical Co. Ltd. of Japan, which has the therapeutic expertise and financial resources to take this technology forward.

I cite these cases to emphasize how combining a solid financial return with a positive human impact in advancing the state of care is the best illustration of what is meant by value investing. To your question, of course there are investments Sofinnova has made that did not have a similarly happy ending. I don’t think there are any tangible lessons we can learn from these – the factors in each case tend to be different. The randomized clinical trial [RCT] is a Pandora’s box – and sometimes you open it to find that the data don’t hold up. Estimates of market size and demand fall short. These are the risks you take in betting on new research many years in advance of commercialization. What is much more painful is the encounter with poor management or leaders who are headstrong and unwilling to adapt. If you fail to take action early enough, things can get quite ugly. As an investor, I’ve encountered this kind of situation more than a few times in my career. But on balance I have had more successes than failures. This explains why I am still here today.

**Investment Hot Spots**

**Looking further at the science of medicine, what does the VC landscape look like today? What are the hot sectors of the moment and what are you most excited about?**

There are innumerable opportunities in science today, versus only a few years ago. In CNS research, I am excited about the progress in understanding what causes neurodegenerative diseases. Only five years ago, raising this therapeutic area would have elicited a chorus of negatives from biopharma: too scary, too early to address, with too few prospects for success. There were scant examples of big pharma putting money into early-stage deals. Today, we see that the science has evolved. Biomarkers are being developed to provide a clearer line of sight to establish the efficacy of compounds for testing in trials. We expect some important breakthroughs in the next several years on neurodegeneration, even in the midst of a continuing lack of progress in Alzheimer’s disease research. An example is treatment for progressive supranuclear palsy [PSP], a debilitating condition caused by nerve cell damage, mostly in the elderly. I also note the growing interest in drugs that inhibit cerebral amyloid angiopathy [CAA], which is caused by the same amyloid protein associated with Alzheimer’s dementia and thus could assist in addressing this major long-term threat too.

There is also the progress in immuno-oncology, a complex field with many promising therapeutic pathways but also posing enormous logistical and manufacturing demands that companies must solve. We look for companies that have the edge on that. Finally, the team at Sofinnova is looking at the potential of immunology in general. Scientists are adding substantive knowledge to fields like immuno-metabolism or the inflammasome, as well as confirming the manifold ways the human immune system interacts with the microbiome in the gut. Although the research appears esoteric, we notice it is attracting a lot of attention from the commercial side, motivated by the opportunity to bring these new innovations to patients.

As an equity investor, what is your assessment of the impact of new data technologies like artificial intelligence and machine learning? Will these platforms lead to a transformation in research and the practice of medicine, or are the prospects over-hyped?

AI is an emerging platform. It deserves the attention of serious investors, even if it has been over-hyped for use in biopharma today. It may be our duty to invest, but, more importantly, we must derive some return as well. And right now, from that perspective, we think the jury on AI is still out. But we are examining with a microscopic intensity where in AI we wish to play. A key area we’ve identified is in digital therapeutics, where the potential of AI is huge, whether it’s an app or an algorithm that provides a clear picture of disease and gives the patient a measure of control over a condition.

**Investing Strategy: Data Versus Divination**

What is your approach when evaluating an investment opportunity? Do you rely principally on rigorous evaluation based on facts and data, or is it that sixth sense – relying on the hunch, gut instinct and experience – the dominant trait?

Our decision-making framework is built around the concept of the puzzle. Consider we are all looking at 10,000 pieces of a puzzle that is a portrait – Da Vinci’s Mona Lisa. Now you could use a spectroscopy device to scan each one of the pieces, but what would it tell you beyond the finest level of detail for each of them? It would not by itself show you it’s part of the Mona Lisa. That requires a slow, steady step-wise process: what you learn about the first thousand pieces may allow you to move to the next four thousand. This is the role that facts and figures play when we consider an investment – it’s a confirmatory and
confidence-building application.

At the end of the day, however, the investor must match this with what is felt in the gut. When you put the two strands together, you are almost there. The last step is measuring the degree of conviction behind a deal. Investors on our team need to calmly marshal the facts – and if after that they don’t jump up or pound on the table, then the deal doesn’t go through. It’s simple: decisions on investment involve so much uncertainty that we want all our colleagues to be fully committed. When facts fail the test of certainty, which is very difficult in this business, you have to go with a feeling.

Alternatively, are there any red flags that require you to walk away from an investment?

If the management of a company that wants us to invest cannot present a simple, factual and coherent message on why we should take a stake – well, that’s a problem. If the business proposition is clear, it’s OK if a potential partner cannot answer a question up front. It’s actually a point of favor if you can admit what you don’t know. But the red flag comes up when management presents as all-knowing but is really evasive or seeking to deceive. The element of trust, so critical to an investment relationship, is destroyed in an instant. No one pitching to Sofinnova recovers from that.

China’s Competitive Challenge

What do you see next for Sofinnova as an investor? Where will you and the company be five years from now? Any comments on government industrial policy to advance the future of VC in Europe?

I will put it bluntly: France is one of the best locations in Europe to set up a biotech company. I am not biased. I say this simply because I believe that in the next five years government policies in Europe will have minimal impact on the progress of the local VC community. It’s a micro issue. The European Union Commission’s new VentureEU fund is helpful but it cannot fully replace the role of a dynamic private sector able to generate capital on its own.

The important, macro issue is the competitive positioning of Europe against the US and China. This has much to do with business basics like financial strength and market size and scale. I’ve spent considerable time in China over the past 10 years, but I have never been more aroused by what I see going on there now – good and bad. Anyone doing due diligence in China knows the country is making an enormous strategic commitment to health care for its 1.3 billion people, especially in promoting biomedicines as a driver of homegrown innovation. Ten years ago there was no innovation in China; today, we are seeing a reverse diaspora of talent coming home to support the academic establishment and contribute expertise learned abroad at dozens of well-funded research institutes and emerging start-up companies.

Sofinnova has no plans to jump full-scale into the Chinese capital investing market. Europe is our prime turf and it will remain so. Nevertheless, China is incorporated in our company strategy going forward. It is realistic to assume our biotech and med tech client pool will have more options in securing funding or partners to grow their businesses. Already, the emergent Hong Kong financial market is vying for a share of the IPO and VC investing business not only in China, but with US and Europeans as well. Some of my colleagues in Europe are still thinking in the lexicon of the past, assuming the old regional ties won’t fray. I am persuaded of the opposite: China will pose a challenge to Sofinnova’s standard operational plan for the next decade. We have no choice but to pursue a global strategy, one where we encounter Chinese financing competition in Europe, where we engage Chinese companies as collaborators and co-investors, and as we seek to profit from rising M&A activity involving the Chinese and our European biotech partners.

Finally, the comparative advantage of nations is becoming more prominent as global markets in life sciences converge. In this climate, government policies can hurt, arguably even more than they can help. And Europe has some geopolitical issues that we, as investors, cannot control. One new development that worries us in Europe is the trend toward national security protectionism in the US. The Treasury Department’s Committee on Foreign Investment in the US [CFIUS] has been granted expanded powers by Congress to review foreign company stakes in “critical technology sectors,” including biopharma. In that regard, it was troubling to see its December 2018 ruling failing to completely clear Novartis AG’s $2.1bn acquisition of the Indiana-based biotech company Endocyte Inc. No reason was cited for the decision and the transaction is free to proceed, at least for now. The point is VC investors don’t like uncertainty, so it would be bad for the entire industry if this kind of ruling becomes the norm.

Do you expect to be investing in different areas of science compared with today? What about adjacent sectors to the life sciences?

Sofinnova is exploring opportunities in industrial biotechnology, which takes us beyond addressing the unmet clinical need in health care. We’ve just launched a new €125m fund, Industrial Biotech I, to invest in the societal benefits from adjacent products extracted from the nature biomass rather than on products derived from petroleum and chemicals. In addition, we recently launched a fund, Sofinnova Telethon, dedicated to advancing innovations in gene and cell therapy as well as orphan drugs for rare diseases. The fund, based in Milan, is administered jointly with the Fondazione Telethon, a charitable organization that is Italy’s second-largest independent research institute, which has a 20-year record of expertise in this therapy class. We have great hopes for its success.
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An Interview With KSQ’s David Meeker

David Meeker, a physician by training from a critical care speciality, worked at the Cleveland Clinic during the first part of his career before joining industry through the company Genzyme in 1994. He held many roles at the biotech and after it was acquired by Sanofi, Meeker led Genzyme as a subsidiary business for six years. Now though, he is CEO of KSQ Therapeutics, a biotech founded in 2015 with a focus on CRISPR-enabled functional genomics.

In an exclusive interview, Meeker talks more about 2015-founded KSQ, where the company is heading, and his hopes for and hang-ups about the biotech sector as it moves into 2019.

In Vivo: What attracted you to join KSQ?

David Meeker: There were two main reasons. One, our industry suffers from abysmal failure rates. It is amazing that people are willing to invest given the low probabilities of success here. If you look back there are cases where we could have been better informed and done better. It is still a high-risk endeavor but there are things we could know with better knowledge going in. Currently, when you run an experiment you read the literature, you think you understand the biology, you test a hypothesis, you see some activity and it confirms your hypothesis, and then you carry on down that road. What you haven’t answered in that scenario is what you don’t know. The KSQ approach is to start with no bias. In our case we are looking for targets, gene targets, to develop drugs against. You experiment by saying, “We’re going to screen all 20,000 genes.” We’re not going to say, “We think this gene is important” and test that gene.

KSQ Therapeutics, founded in 2015, is using CRISPR-enabled functional genomics to develop a pipeline of immuno-oncology and targeted oncology therapies.

In an exclusive interview with In Vivo, CEO David Meeker discusses his big pharma background and how he has adapted his strategies to play the game in biotech.

Meeker also discusses KSQ’s R&D goals in 2019, and the company’s approach to partnering in the oncology space.
We’re just going to do all 20,000 and then let the best candidate, the best target new gene, emerge from that complete data set.

We are using a much later generation approach of CRISPR/Cas9 to enable this 20,000-gene screening approach. It has been quite powerful and has yielded some interesting findings. So, that was the first piece.

Then the second attraction, as always, was the quality of the people and what the group had accomplished already. Frank Stegmeier, our CSO, led oncology drug discovery for Novartis prior to coming to KSQ. He had worked a lot on genomics there. With CFO John Trzupek, the two of them have really built a remarkable team and accomplished a huge amount in a short period of time.

What were the biggest changes you felt when moving from a big pharma company to a younger, smaller biotech?

For me, this industry is not about big versus small. We were a team of 35 when I joined just over a year ago, but we have doubled in size, which is rapid growth. Of course, we are still an incredibly small team; however, we have 150 full-time equivalents working on our projects through more than 30 different CROs. The point being, in today’s world, you can access almost everything you need as a small company through those kinds of networks. The advantage of a large company of having their own internal science resources has been largely neutralized. It’s one of those things that conceptually we all might understand but experiencing it is different – I have seen the nimbleness with others if you do not know yourself. I certainly try to be highly attentive to that in my own personal leadership approach.

The second thing is having a mission. There is no substitute for people who are motivated by the mission. Believing in what they do – that we could cure an individual, maybe a small segment of cancer – that is highly motivating. The leader’s challenge is to connect people with that mission.

For large companies, it is about managing at scale. You cannot run a 100,000-person organization in a highly centralized way. My personal belief, having witnessed it, is that you need to decentralize. You need to empower leaders who are managing smaller parts of the group, otherwise you just jam up at the top and you die. There are different challenges in a small organization. This is all about working with fragile resources, right? You are always trying to balance the piece that you have and the pieces you don’t have and how to meet timelines so that you can continue to raise money. The challenges are different but the qualities that succeed, in either case, are the same.

Along those lines, KSQ raised a substantial amount in a series C financing round last year, why do you think the company was able to attract that level of interest from investors?

It has been an interesting period; the market is open. There has clearly been a disproportionate willingness to fund innovative biotechnology companies and we have benefited from that.

The two biggest recent breakthroughs in oncology, arguably, are the PD-1 class and cellular therapies. KSQ is now asking the question, when you knock out a gene in a T cell, what is the impact on that T cell’s ability to get into the tumor and proliferate? And then in subsequent validation experiments we are looking at how to kill the tumor. While PD-1 works quite well, we have found a number of targets that look like PD-1 and a small number of targets that actually look better than PD-1. Despite important medical breakthroughs of our generation, like PD-1, there is still a huge unmet medical need. PD-1 just opened the door to what was possible; but as we know only 20% to 30% of patients respond and the durability of the response is not uniform, and patients become refractory. We have seen a hint as to the potential in this space, but the unmet need remains massive and KSQ is looking to disrupt that space.

On the cellular side, the stories so far are amazing but there is a huge opportunity to do better, and then by far the biggest need is trying to get cell therapies to work in a solid tumor environment – particularly a PD-1 resistant solid tumor. Companies like Iovance are showing us a hint of efficacy, some early signs of efficacy; where you can target the tumor with your T cell, you have a chance of getting a response. We think we can disrupt here as well.

What key R&D goals have you set out for KSQ in 2019?

We have nine programs in our preclinical pipeline. We have identified targets of interest and we are actively in the process of identifying drug compounds. In the next 18 months, the aim is to have at least one of those as a drug candidate. More immediately, our goal is to do an adoptive cell therapy experiment.

We will take two of our targets, which had superior efficacy to PD-1 in our models, and inhibit both simultaneously (a “dual edit”) in T cells obtained from the patient’s tumor (tumor infl-
trating lymphocytes). The editing will add one step to the expansion phase of the TIL process. Our goal is to be in the clinic with this adoptive T cell therapy approach treating the first patient in the first quarter of 2020.

How are you preparing to grow the company in the years ahead?

We will remain incredibly focused on the drug discovery effort. We have a powerful platform but unless we can translate the knowledge obtained from that platform into therapies we will not have realized its potential. Second, we will be extremely thoughtful about our management of capital. Time is more valuable than money in the setting where you believe your approach can make a real difference to patients. We want to be aggressive in our discovery and development efforts and take calculated risks where it makes sense to accelerate our progress. Finally, we do have a powerful platform and we will continue to invest in its potential expanding carefully into new areas. For example, the logical next step where we have done a significant amount of work already is in the area of autoimmunity.

There is a more practical challenge in the industry... Manufacturing capacity for cell and gene therapies is tight. So, there are simple, practical issues about finding a CMO partner to work with that has capacity. That will be solved, industry is rapidly working to build capacity and it will catch up. But that is a practical near-term element.

Also, cutting-edge technologies are always at risk, not only for what happens within your own experiment but what happens to the field in general. For example, people were doing gene therapy experiments many years ago, but one bad outcome in a gene therapy trial put a deep freeze over gene therapy programs in general. There is always the risk that something could happen in a new area of development that could delay the field. Of course, delays when you are a small company can be devastating.

As a smaller company, what is your approach to partnering?

There are two reasons you partner... One, you partner out of desperation — you need money and therefore you sell the rights to your most valuable asset in order to survive. The second, the strategy everybody would like to pursue, is that you partner when it makes sense.

We clearly have more in our pipeline than we can take forward on our own, so we will partner at some point. My goal is to partner when it makes sense. In this case, that would mean taking what we have forward to proof-of-concept. Once we have defined whether we have a drug or not, it becomes much more straightforward to have a discussion with a potential partner about the value of a program and what a partner could bring to the equation. We would be looking for more in a partnership than money – funding can be raised in different ways – we would be looking for a partner who could bring in something we do not have such as capabilities, experience or reach.

Aside from competition in the IO space, what are your greatest concerns when you look ahead in 2019?

The US health care system is challenged. We can get the best health care in the world in America, we just cannot get it consistently and universally. The ongoing debate around drug pricing has some areas of real concern. I worry that if price controls – structures or legislation – are imposed, it will have a chilling effect on innovation. What people lose sight of is the vast amount of money people are willing to put at risk in this environment, but this is possible because of the potential rewards. However, I am also concerned that we as industry do not universally take a responsible position in the pricing of our products. By that I do not mean pricing for innovative products; it is the year-on-year price increases, with no added value. This practice is not sustainable, and I think it will be damaging to us as an industry in the long term.

What are you looking forward to this year and in the future?

More breakthroughs in gene therapy. I think we are on the cusp of seeing broad breakthroughs in gene therapy, which are going to transform treatment and the health care system. Also, in cancer, cures will come from immuno-oncology. So, despite immuno-oncology fatigue, it is the right scientific approach, and I think we will see the next wave of breakthroughs here and I believe that KSQ will be a part of that.

Email the author: Lucie.Ellis@Informa.com
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## On the Move

Recent executive appointments in the life sciences industry

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<tr>
<td>Marie Kosco Vilbois</td>
<td>AC Immune SA</td>
<td>Chief Scientific Officer</td>
<td>Novimmune</td>
<td>Chief Scientific Officer</td>
<td>3-Jan-19</td>
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<tr>
<td>Scott Megaffin</td>
<td>Adastra Pharmaceuticals</td>
<td>Chief Executive Officer and Director</td>
<td>Churchill Pharmaceuticals LLC</td>
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<td>Andrew Oxtoby</td>
<td>Aimmune Therapeutics</td>
<td>Chief Commercial Officer</td>
<td>Eli Lilly &amp; Co</td>
<td>Vice President, US Diabetes Connected Care</td>
<td>22-Jan-19</td>
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<td>Francesca Domenech Wuttke</td>
<td>Almirall SA</td>
<td>Chief Digital Officer and Management Board Member</td>
<td>Novartis AG</td>
<td>Global Director, Commercial Strategy</td>
<td>4-Jan-19</td>
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<td>Angie You</td>
<td>Amunix Operating Inc</td>
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<td>Sierra Oncology</td>
<td>Chief Business and Strategy Officer and Head, Commercial</td>
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<td>Jay Venkatesan</td>
<td>Angion Biomedica Corp</td>
<td>Chief Executive Officer and President</td>
<td>Alpine Immune Sciences</td>
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<td>John F. Neylan</td>
<td>Angion Biomedica Corp</td>
<td>Chief Medical Officer and Senior Vice President</td>
<td>Keryx</td>
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<td>Gary H. Slatko</td>
<td>Aquestive Therapeutics</td>
<td>Chief Medical Officer and Senior Vice President</td>
<td>FDA</td>
<td>Director, Office of Medication Error Prevention and Risk Management</td>
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<td>Eric B. Mosbrooker</td>
<td>Audentes Therapeutics Inc</td>
<td>Chief Commercial Officer and Senior Vice President</td>
<td>Origin Biosciences</td>
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<td>Eric Sandberg</td>
<td>AxoGen Inc</td>
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<td>Visura Technologies</td>
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<td>Steven Bell</td>
<td>Biocoat Inc</td>
<td>Chief Financial Officer</td>
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<td>Srikanth (Sri) Ramaswami</td>
<td>Caris Life Sciences Ltd</td>
<td>Chief Communications Officer and Vice President</td>
<td>rbb Communications</td>
<td>Executive Vice President</td>
<td>21-Jan-19</td>
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<tr>
<td>Jamie Oliver</td>
<td>ChemioCare</td>
<td>Chief Medical Officer</td>
<td>Accelovance Inc</td>
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<td>7-Jan-19</td>
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<tr>
<td>Darlene Horton</td>
<td>Coherus BioSciences</td>
<td>Chief Medical and Regulatory Affairs Officer</td>
<td>TulangCo Inc</td>
<td>Chief Executive Officer</td>
<td>1-Jan-19</td>
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<tr>
<td>Michael Detke</td>
<td>Cortexyme Inc</td>
<td>Chief Medical Officer</td>
<td>Embera NeuroTherapeutics</td>
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<td>Philip M. Brown</td>
<td>Dermavant Sciences</td>
<td>Chief Medical Officer</td>
<td>Lexicon Pharmaceuticals</td>
<td>Senior Vice President, Clinical Development</td>
<td>2-Jan-19</td>
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<tr>
<td>Bryan E. Stuart</td>
<td>Fulcrum Therapeutics</td>
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<td>Yarra Therapeutics</td>
<td>Chief Executive Officer and President</td>
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<td>Misbah Tahir</td>
<td>IGM Biosciences Inc</td>
<td>Chief Financial Officer</td>
<td>Dermira Inc</td>
<td>Vice President, Head, Finance</td>
<td>3-Jan-19</td>
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<tr>
<td>Ivan Plavec</td>
<td>ImaginAb Inc</td>
<td>Chief Business Officer and Independent Non-Executive Director</td>
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<td>2-Jan-19</td>
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<tr>
<td>Thomas A. Shea</td>
<td>ImmusanT Inc</td>
<td>Chief Financial Officer</td>
<td>Albireo Pharma</td>
<td>Chief Financial Officer</td>
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<tr>
<td>Jason Marks</td>
<td>InflaRx GmbH</td>
<td>Chief Legal Officer and General Counsel</td>
<td>Bausch Health</td>
<td>Chief Legal Officer and General Counsel</td>
<td>3-Jan-19</td>
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<tr>
<td>Jordan Silverstein</td>
<td>InflaRx GmbH</td>
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<td>Advanced Accelerator Applications</td>
<td>Head, Corporate Strategy and Development</td>
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<tr>
<td>Wayde McMillan</td>
<td>Insulet Corp</td>
<td>Chief Financial Officer and Executive Vice President</td>
<td>Medtronic</td>
<td>Chief Financial Officer and Vice President, Minimally Invasive Therapies</td>
<td>1-Mar-19</td>
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<tr>
<td>Michael Shetzline</td>
<td>Ironwood Pharmaceuticals Inc</td>
<td>Chief Medical Officer, Senior Vice President and Head, Drug Development</td>
<td>Takeda Pharmaceuticals International Co</td>
<td>Vice President and Head, Gastroenterology Clinical Sciences</td>
<td>28-Jan-19</td>
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<tr>
<td>Robert Schueren</td>
<td>Natera Inc</td>
<td>Chief Operating Officer</td>
<td>IntegenX Inc</td>
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### COMPANY CHANGES

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<tr>
<td>Fatih Uckun</td>
<td>Oncotelic Inc</td>
<td>Chief Medical Officer</td>
<td>Ares Pharmaceuticals</td>
<td>Head, Immuno-Oncology</td>
<td>22-Jan-19</td>
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<tr>
<td>Neil H. Shusterman</td>
<td>Palladio Biosciences</td>
<td>Chief Medical Officer</td>
<td>Endo Pharmaceuticals Inc</td>
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<td>3-Jan-19</td>
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<tr>
<td>Clinton Musil</td>
<td>Personalis Inc</td>
<td>Chief Business Officer</td>
<td>ARMO Biosciences</td>
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<tr>
<td>Asha Das</td>
<td>Progenics Pharmaceuticals Inc</td>
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<td>Tocagen</td>
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<tr>
<td>Eric Dube</td>
<td>Retrophin Inc</td>
<td>Chief Executive Officer and President</td>
<td>ViIV Healthcare</td>
<td>President, North America</td>
<td>3-Jan-19</td>
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<tr>
<td>Lyn Baranowski</td>
<td>Roivant Sciences Inc</td>
<td>Chief Operating Officer, Altavant Sciences</td>
<td>Melinta Therapeutics</td>
<td>Senior Vice President, Corporate Development and Strategy</td>
<td>2-Jan-19</td>
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<tr>
<td>Samantha Paston</td>
<td>Scancell Ltd</td>
<td>Head, Research</td>
<td>Immunocore</td>
<td>Head, T Cell Cloning</td>
<td>15-Jan-19</td>
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<tr>
<td>Oliver Rosen</td>
<td>SQZ Biotech</td>
<td>Chief Medical Officer</td>
<td>Deciphera Pharmaceuticals Inc</td>
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<td>3-Jan-19</td>
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<tr>
<td>Moon Hee-Seok</td>
<td>Takeda Pharmaceuticals Korea</td>
<td>Chief Executive Officer</td>
<td>Shire Korea</td>
<td>Chief Executive Officer</td>
<td>15-Jan-19</td>
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<tr>
<td>Tony Kingsley</td>
<td>TARIS BioMedical LLC</td>
<td>Chief Executive Officer, President and Director</td>
<td>The Medicines Company</td>
<td>President and Chief Operating Officer</td>
<td>3-Jan-19</td>
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<tr>
<td>Nora Brennan</td>
<td>TELA Bio</td>
<td>Chief Financial Officer</td>
<td>Xeris Pharmaceuticals Inc</td>
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<td>2-Jan-19</td>
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<tr>
<td>Claudia D’Augusta</td>
<td>Therachon AG</td>
<td>Chief Financial Officer</td>
<td>TiGenix NV</td>
<td>Chief Financial Officer</td>
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<tr>
<td>Scott Clarke</td>
<td>Tizona Therapeutics Inc</td>
<td>Chief Executive Officer</td>
<td>Roche</td>
<td>Global Head, Oncology Partnering and Head, Asia and Emerging Markets Partnering</td>
<td>3-Jan-19</td>
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### PROMOTIONS

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<tr>
<td>Patrick S. Miles</td>
<td>Alphatec Holdings Inc</td>
<td>Executive Chairman, Chief Executive Officer and President</td>
<td>Executive Chairman and Chief Executive Officer</td>
<td>7-Jan-19</td>
</tr>
<tr>
<td>Andrew Sassine</td>
<td>Arcturus Therapeutics Ltd</td>
<td>Chief Financial Officer and Director</td>
<td>Interim Chief Financial Officer and Director</td>
<td>1-Jan-19</td>
</tr>
<tr>
<td>Gary Wilcox</td>
<td>Cocrystal Pharma Inc</td>
<td>Chairman and Chief Executive Officer</td>
<td>Chief Executive Officer</td>
<td>1-Feb-19</td>
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<tr>
<td>Christina Willwerth</td>
<td>Flexion Therapeutics</td>
<td>Chief Strategy Officer</td>
<td>Senior Vice President, Management and Strategy</td>
<td>22-Jan-19</td>
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<tr>
<td>Mai-Jing Liao</td>
<td>Harbour BioMed</td>
<td>Chief Business Officer</td>
<td>Senior Vice President and Head, Business Development and Portfolio Management</td>
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<tr>
<td>Xiaoxiang Chen</td>
<td>Harbour BioMed</td>
<td>Chief Development Officer</td>
<td>Executive Vice President and Head, Clinical Development and Regulatory Science</td>
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### EXECUTIVES ON THE MOVE

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<tr>
<td>Isaac Ciechanover</td>
<td>Atara Biotherapeutics Inc</td>
<td>Chief Executive Officer</td>
<td>Senior Vice President, Finance and Operations</td>
<td>30-Jun-19</td>
<td>Resignation</td>
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<tr>
<td>Peter S. Roddy</td>
<td>Cytokinetics Inc</td>
<td>Chief Accounting Officer and Senior Vice President</td>
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<td>31-May-19</td>
<td>Retirement</td>
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<tr>
<td>Kalevi Reijonen</td>
<td>FIT Biotech Oy</td>
<td>Chief Medical Officer and Senior Vice President</td>
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<td>1-Jan-19</td>
<td>Retirement</td>
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<tr>
<td>Michael Falvey</td>
<td>Karyopharm Therapeutics</td>
<td>Chief Financial Officer, Executive Vice President and Treasurer</td>
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<td>18-Jan-19</td>
<td>Resignation</td>
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<tr>
<td>Nathan Stasko</td>
<td>Novan</td>
<td>President</td>
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<td>Resignation</td>
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<tr>
<td>Ron Bentsur</td>
<td>UroGen Pharma</td>
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<tr>
<td>Mats Blom</td>
<td>Zealand Pharma AS</td>
<td>Chief Financial Officer</td>
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<td>Steve Chapman</td>
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<td>Holly Whittemore</td>
<td>Nimbus Therapeutics</td>
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<td>Elizabeth Messersmith</td>
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<td>Chief Development Officer</td>
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<td>Paula Brown Stafford</td>
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<td>Amy Vandenberg</td>
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<td>Kelly Huang</td>
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<td>Leigh Elkolli</td>
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<td>Philip Kuo-Lung Huang</td>
<td>TaiGen Biotechnology Co Ltd</td>
<td>Chairman, Chief Executive Officer, President, Chief Commercial Officer, General Manager and Member of Steering Committee</td>
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<tr>
<td>Mark Hensley</td>
<td>Veloxis Pharmaceuticals AS</td>
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### DIRECTORS

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<tr>
<td>Nicole Vitullo</td>
<td>Achillion Pharmaceuticals Inc</td>
<td>Chairman</td>
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<tr>
<td>Chris Brinsmead</td>
<td>Consort Medical plc</td>
<td>Director</td>
<td>7-Feb-19</td>
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<tr>
<td>Juhani Pitkäkoski</td>
<td>FIT Biotech Oy</td>
<td>Director</td>
<td>3-Jan-19</td>
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<td>Paula Brown</td>
<td>Novan</td>
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<td>Philip Kuo-Lung Huang</td>
<td>REVA Medical Inc</td>
<td>Chief Financial Officer and Corporate Secretary</td>
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<td>Mark Hensley</td>
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<tr>
<td>Holly Whittemore</td>
<td>Nimbus Therapeutics</td>
<td>Chief Financial Officer</td>
<td>Senior Vice President, Finance and Operations</td>
<td>3-Jan-19</td>
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<td>Elizabeth Messersmith</td>
<td>Novan</td>
<td>Chief Development Officer</td>
<td>Senior Vice President, Clinical Operations</td>
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<tr>
<td>Paula Brown Stafford</td>
<td>Novan</td>
<td>Chief Operating Officer, President and Director</td>
<td>Chief Development Officer and Director</td>
<td>2-Jan-19</td>
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<tr>
<td>Amy Vandenberg</td>
<td>Obalon Therapeutics</td>
<td>Chief Clinical and Regulatory Affairs Officer</td>
<td>Vice President, Clinical and Regulatory Affairs</td>
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<td>Kelly Huang</td>
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<td>President</td>
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<td>Leo Lee</td>
<td>Regeneus Ltd</td>
<td>Chief Executive Officer and Director</td>
<td>Director</td>
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<td>Leigh Elkolli</td>
<td>REVA Medical Inc</td>
<td>Chief Financial Officer and Corporate Secretary</td>
<td>Senior Director, Finance and Corporate Controller</td>
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<td>Philip Kuo-Lung Huang</td>
<td>TaiGen Biotechnology Co Ltd</td>
<td>Chairman, Chief Executive Officer, President, Chief Commercial Officer, General Manager and Member of Steering Committee</td>
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<td>Mark Hensley</td>
<td>Veloxis Pharmaceuticals AS</td>
<td>Chief Commercial Officer</td>
<td>Vice President, Sales</td>
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### EXECUTIVE FROM COMPANY PREVIOUS ROLE EFFECTIVE DATE

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<td>Michael Falvey</td>
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<td>Nathan Stasko</td>
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<td>Ron Bentsur</td>
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<td>Mats Blom</td>
<td>Zealand Pharma AS</td>
<td>Chief Financial Officer</td>
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Deal-Making
Covering deals made January 2019

IN VITRO DIAGNOSTICS
ALLIANCES
J&J, Veracyte ally in lung cancer diagnostics

FINANCINGS
Biocartis closes oversubscribed €55.5mm PIPE

MEDICAL DEVICES
MERGERS & ACQUISITIONS
Abbott exercises option to acquire Cephea Valve
Medtronic acquires EPIX Therapeutics

ALLIANCES
Circassia gets US and Chinese rights to AIT’s pulmonary hypertension system
Otsuka pays up to $302mm for license to Click’s CT152 for MDD

FINANCINGS
Brainsway again attempts IPO on Nasdaq
ConMed issues $345mm of its convertible senior notes

PHARMACEUTICALS
MERGERS & ACQUISITIONS
Bristol-Myers Squibb acquires Celgene for $74bn, deepening strength in oncology
AmpliPhi, C3J reverse merge
Lilly buys Loxo for $8bn cash

ALLIANCES
AbbVie, Coherus settle Humira biosimilar patent litigation
AbbVie gets option to Tizona’s cancer antibody
Acer licenses osanteman from Sanofi
Genentech partners with Adaptive on neoantigen-directed T-cell therapies
Alexion acquires 19.9% stake in Caelum through CAEL101 co-development pact; holds option to acquire company outright
Allergan/Ironwood settle generic Linzess patent litigation with Mylan
Kowa Pharmaceuticals gets US co-promote rights to Allergan’s Bystolic
Teva settles patent litigation with Amgen over generic cinacalcet
Alphamab grants Asclelis rights to HBV candidate in Greater China
Biogen, C4 partner to develop CNS therapies
Biogen, Skyhawk team up in the CNS space
Boehringer and Bioharmony partner to develop therapies for bacterial infections
BioTime, Orbit Biomedical team up in dry-AMD
BI partners with Science 37 for the development of novel therapies
BI partners with Vanderbilt for novel psychiatric therapies
CANbridge to commercialize GC Pharma’s Hunterase in China
Celgene gets options to Kyn’s I/O therapies
Celgene options cell therapies from Obsidian
Celgene and Triphage pen new deal for leukemia therapy
Codiak and Jazz team up to develop exosome therapies for cancer
CytoReason teams up with Pfizer in drug discovery
Denali, SIRION collaborate on AAV gene therapies for neurodegenerative diseases
Everest gets certain Asian rights to Spero antibiotics
Roche to use Exscientia’s Centaur Chemist to identify preclinical candidates
Fedora, Meiji Seika form NacuGen joint venture
Ferring gains US license to Sun’s generic gani-relax acetate for premature ovulation
Galapagos gets global rights Fibrocor’s small-molecule inhibitor program
Gilead gets NASH rights from Yuhan; pays up to $785mm
Grifols to sell fostamatinib in Europe for Rigel
Lundbeck, Numerate collaborate on AI-based CNS therapeutics discovery
HemoShear, Horizon team up to develop gut therapies
Janssen, MeiraGTx ally in the gene therapy space for retinal diseases
Knight gets Canadian rights to Puma’s Nerlynx
Mersana gets nonexclusive license to SynAffix’s GlycoConnect ADC technology
Neurocrine licenses up to four Voyager neuro programs in $1.9bn collaboration
Oculis gains license to Novartis’ LME636 for ophthalmic conditions
Purdue evaluates Ocular’s delivery technology in non-opioid therapeutics
Purdue licenses Alivio’s ALV107 for IC/BPS pain
ScPharma, West team up in drug delivery pact

FINANCINGS
Acceleron nets $216.2mm via FOPO
Aimmune enters $170mm loan agreement; gets $40mm up front

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888-670-8900 or PharmaNewsSales@informa.com

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.
Alnylam nets $382.3mm via FOPO

Private placement brings in $25mm for Alpine Immune

Anchiano files for US initial public offering

Bellerophon nets $6.5mm via FOPO

Coherus BioSciences secures $75mm credit facility

Kaleido Biosciences seeks to go public

Mirati nets $108mm through follow-on offering

Poseida Therapeutics files for initial public offering

Public offering nets $200mm for PTC Therapeutics

Revance FOPO nets $94mm

Selecta Bio nets $28.2mm via FOPO

Uroseda public offering nets $86.5mm for Stemline

Sunesis nets $18.8mm through public offerings of common and preferred shares

Urogen nets $141mm through follow-on offering

Wave Life Sciences nets $141mm in FOPO

## IN VITRO DIAGNOSTICS

### ALLIANCES

**JOHNSON & JOHNSON VERACYTE INC.**

Johnson & Johnson and Veracyte Inc. are teaming up in the development of two nasal swab tests for early lung cancer detection. (Jan.)

Johnson & Johnson will provide Veracyte with non-exclusive rights to samples and clinical data for use in the development of a next-generation bronchial genomic classifier diagnostic (Percepta) and a nasal genomic classifier diagnostic (NasaRISK) for lung cancer. J&J will pay $5mm up front and up to $15mm in development and reimbursement milestones tied to Percepta v.2 and NasaRISK. For ten years, beginning on the first commercial sale of the products, Veracyte will pay J&J 1% royalties on Percepta v.2 and in the low-single-digits for NasaRISK. The Lung Cancer Initiative at J&J and Veracyte will combine clinical study cohorts with more than 5,000 patients.

Veracyte will contribute bronchial and nasal samples from its trials and perform whole-transcriptome sequencing on the entire cohort. Veracyte will have exclusive rights to all the findings resulting from the collaboration and is granting J&J a non-exclusive license to use data generated for therapeutic purposes and to develop a companion diagnostic for use with a J&J therapeutic. When used with bronchoscopy, Percepta detects lung nodules with 97% sensitivity. It could launch in H1 2019.

### FINANCINGS

**BIOCARTIS NV**

Biocartis NV raised €5.5mm ($63mm) through an oversubscribed private placement of 5mm new shares at €11.10 apiece (an 8% discount). Funds will support expansion of the Idylla test menu and applications. The fully automated real-time PCR system’s menu currently includes tests for melanoma, lung, and colorectal cancers, with assays available for both solid and liquid samples. Proceeds will also go towards sales and marketing activities, manufacturing, and working capital. (Jan.)

Investment Banks/Advisors: Joh. Berenberg, Gossler & Co. KG; KBC Securities; Kempen & Co.

## MEDICAL DEVICES

### MERGERS & ACQUISITIONS

**ABBOTT LABORATORIES INC. CEPHEA VALVE TECHNOLOGIES INC.**

Abbott Laboratories Inc. exercised its option to acquire private cardiovascular device maker Cephea Valve Technologies Inc. for an undisclosed sum. (Jan.)

Abbott got the option under a mid-2015 deal when it made an undisclosed equity investment in Cephea. Cephea is developing a catheter-based mitral valve replacement as an option for patients who need to have their diseased mitral valves replaced. The artificial valve can be delivered through a vein in the leg. There are currently no transcatheter mitral valve replacement devices on the market. The purchase of Cephea gives Abbott expanded presence in the mitral valve space. It currently sells MitraClip which helps repair a damaged valve but not replace it. (Abbott gained the device through its 2009 acquisition of Evalve.) At the recently held JP Morgan Healthcare Conference, Abbott stated that it is investing a lot in the structural heart space and is expecting $1bn in sales during 2019 as mitral valve conditions are more prevalent than ever. MitroClip is the key product in this business and generates about $500mm in sales alone.

**MEDTRONIC PLC**

**EPIX THERAPEUTICS INC.**

Expanding its cardiac ablation portfolio, Medtronic PLC is acquiring private cardiovascular device maker Epix Therapeutics Inc. (formerly Advanced Cardiac Therapeutics) for an undisclosed sum. (Jan.)

Epix has developed the DiamondTemp temperature-controlled ablation system that consists of a catheter, radiofrequency (RF) generator, and integrated fluid irrigation pump for treating patients with cardiac arrhythmias, including atrial fibrillation. The closed-loop system uses RF (heat) energy to create scar tissue in the heart via a minimally invasive approach and provides physicians with high-resolution electrogams to improve treatment for AF patients. DiamondTemp received the CE Mark in 2017 and is currently in clinical trials in the US. One trial
completed enrollment in October 2018 for symptomatic paroxysmal AF and another is currently enrolling patients with persistent AF. The system is complementary to Medtronic’s own cryoballoon technology that uses cryo (cold) energy to isolate the pulmonary veins. Having both technologies, Medtronic can offer a complementary suite of products for cardiac patients.

**ALLIANCES**

**AIT THERAPEUTICS INC.**

**CIRCASSIA PHARMACEUTICALS PLC**

AIT Therapeutics Inc. licensed Circassia Pharmaceuticals PLC commercial rights in the US and China to its AirNOvent cylinder free nitric oxide (NO) generator and phasic-flow delivery system for use in treating persistent pulmonary hypertension of the newborn (PPHN) and related indications in the hospital setting. (Jan.) Circassia will pay AIT $7.35mm up front and cost plus for generator systems and filters. In addition, it will shell out milestones either in cash or Circassia stock (at a discount to a pre-determined trailing average) as follows: $3.15mm upon successful completion of an FDA pre-submission meeting (expected in February 2019); $12.6mm on the sooner of 90 days post FDA approval or US launch; $8.4mm upon label expansion beyond PPHN in the US; and $1.05mm on product launch upon label expansion beyond PPHN in China. AIT is also eligible for royalties as follows: a 5% royalty on first cumulative $20mm in US gross profit; a 5% royalty on first cumulative $50mm in US gross profit; a 5% royalty on first cumulative $20mm in China gross profit; and a 20% royalty for over $100mm in annual gross profit (US and China combined). AIT will be responsible for all development, manufacturing, and cost plus for generator systems.

**FINANCINGS**

**BRAINSWAY LTD.**

Brainsway Ltd. (deep transcranial magnetostimulation device (TMS) for psychiatric, neurological, and addiction disorders) is making a second attempt to list on Nasdaq through an initial public offering of American Depositary Shares (ADSs). (Jan.) Investment Banks/Advisors: Cantor Fitzgerald & Co.

**CONMED CORP.**

ConMed Corp. (minimally invasive surgical devices) grossed $345mm (including the overallotment) through the issuance to private investors of 2.625% senior notes due 2024. The notes convert to common at 11.2608 shares per $1k principal amount, or $88.80 per share. (The company’s stock averaged $65.31 at the time of placement.) ConMed will use about $18mm of the proceeds to pay the cost of certain convertible note hedge transactions, and will also put the funds towards its upcom

**CLICK THERAPEUTICS INC.**

**OTSUKA HOLDINGS CO. LTD.**

Otsuka Pharmaceutical Co. Ltd. will ally with Click Therapeutics Inc. to develop and commercialize the latter’s mobile software application CT152 as a prescription digital therapeutic for major depressive disorder (MDD) to treat patients either independently or in conjunction with other prescribed pharmaceuticals. (Jan.) Click will receive funding from Otsuka for development of its mobile software application CT152, which combines evidence-based cognitive therapy principles and Click’s AI-powered Clickometrics patient engagement platform. Otsuka will commercialize CT152 on a worldwide basis upon regulatory approval in exchange for up to $10mm in up-front and regulatory milestone payments, an estimated $20mm in development funding, $272mm in commercial milestones, and tiered, double-digit royalties on global sales of resulting software and digital therapeutic applications. The alliance draws upon Otsuka’s expertise in development and commercialization of mental health therapeutics and Click’s digital technologies and strengths in discovery and validation of software applications. The Clickometrics data science platform is a personalized neurobehavioral intervention tool engineered using statistical algorithms to recommend the best, clinically validated methods based on the cognitive and behavioral mechanisms of each individual patient. CT152, which is expected to soon begin a multi-center, randomized Phase III trial, will fall under the software as a medical device (SaMD) classification and be subject to the FDA regulatory framework supporting commercialization of digital tools.

**Mergers & Acquisitions**

**BRISTOL-MYERS SQUIBB CO.**

**CELGENE CORP.**

In the fourth-largest biopharma acquisition to date, Bristol-Myers Squibb Co. bought top-tier public biotech Celgene Corp. for $74bn. For each Celgene share, BMS will issue one of its shares (valued at $50 each) and pay $50 in cash, equating to a per-share price of $100, or a 58% premium. Celgene also gets one tradeable contingent value right (CVR) for each of its shares, providing additional payments of $9 in cash based on regulatory milestones. At closing, BMS stockholders will own 69% of the combined entity, and Celgene shareholders the rest. (Jan.) In deal value, the BMS/Celgene transaction is only behind Glaxo and SmithKline from 2000 ($78bn), Takeda and Shire from 2018 ($79bn), and Pfizer and Warner-Lambert from 1999 ($84bn). Founded in 1986, Celgene has built itself through internal R&D investment as well as a strong focus on biotech partnering and acquisition. As a result, it brings BMS complementary assets in the oncology, immunology, and inflammation areas. Combined with BMS’s work in cardiovascular disease, these represent the major categories of the new combined company. Celgene’s biggest deals have included the $9bn takeover of CAR-T player Juno in 2018, the $7bn acquisition of Receptos (which brought Celgene the potential next-generation immunofluorescence compound ozanimod), and the $2.9bn acquisition of Abaxis BioScience, the maker of Abraxane, now one of Celgene’s key oncology products for various solid tumors. (The CVRs are tied to the FDA approvals of Juno’s lisocabtagene maraleucel by December 31, 2020, for relapsed/refractory diffuse large B-cell lymphoma; ozanimod by December 31, 2020, for relapsing multiple sclerosis; and bb2121 [from an alliance with bluebird bio] by March 31, 2021, for relapsed/refractory multiple myeloma.) In addition to Abraxane, Celgene’s other major cancer drugs are Revlimid for multiple myeloma and myelodysplastic syndrome (expected to face generic competition in 2022), and Pomalyst for multiple myeloma. Several of Celgene’s oncology treatments have been paired with immuno-oncology agents in the past, including with BMS’s Opdivo and Merck & Co.’s Keytruda. Owning Celgene would now give BMS control of those combinations, should they succeed. Potential future big products for Celgene include luspatercept (thalassemia and myelodys-

**PHARMACEUTICALS**

**Deals-Making**

**In Vivo | February 2019**
plastic syndrome) and fedratinib (myelofibrosis). In 2017, Celgene reported $13bn in revenue and $2.9bn in net income, and had $2.5bn cash on hand at the end of Q3 2018. Investment Banks/Advisors: Citigroup Inc.; JP Morgan & Co. (Celgene Corp.); Evercore Partners; Morgan Stanley & Co. (Bristol-Myers Squibb Co.)

C3J THERAPEUTICS INC. AMPPLIFI BIOSCIENCES CORP. AmpliPhi Biosciences Corp. is reverse merging with fellow infectious disease-focused firm C3J Therapeutics Inc. in a stock swap. (Jan.) At the signing of the agreement, closely held C3J ($28m valuation) will hold a 70% stake in the merged entity with publicly traded AmpliPhi ($122m valuation) owning the remaining 30%. When the deal officially closes, C3J will invest $10m in the combined company to help fund development of preclinical and clinical programs. Following the financing, the new firm will trade on the NYSE American, is expected to have a cash balance of $18m, and will be owned 76%/24% by C3J and AmpliPhi, respectively. C3J CEO Todd Patrick, C3J Chief Development Officer Brian Varnum, and AmpliPhi CFO Steve Martin will all retain their positions. The board will consist of five members designated by C3J Therapeutics and two by AmpliPhi. The merged company will be a leader in the development of targeted bacteriophage therapeutics. AmpliPhi will contribute its broad phage library, Phase I/II-ready AB-SA01 targeting Staphylococcus aureus, AB-PA01 against Pseudomonas aeruginosa (expected to enter the clinic later this year), and preclinical programs. C3J adds its STAMPS (Specifically Targeted AntiMicrobial Peptides) technology that can re-engineer the human microbiome by selectively eliminating Keystone pathogens that drive microbial dysbiosis, its synthetic bacteriophage platform, and preclinical antimicrobial pipeline. Investment Banks/Advisors: Ladenburg Thalmann & Co. Inc. (AmpliPhi BioSciences Corp.;) LifeSci Advisors: Ladenburg Thalmann & Co. Inc.

ELI LILLY & CO. LOXO ONCOLOGY INC. Eli Lilly & Co. will acquire Loxo Oncology Inc. (treatments for genomically-defined cancers) for $235 per share in cash (a 74% premium to Loxo’s market average in the ten days prior to the announcement), or approximately $8bn. (Jan.) Through the deal, Lilly gets access to Loxo’s marketed oral TRK inhibitor Vitrakvi (larotrectinib), approved by the FDA in November for adults and children with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion. The drug was developed in collaboration with Bayer, and is the first approved treatment that targets a specific genetic abnormality to receive a tumor-agnostic indication by the FDA. Loxo’s pipeline also includes LOXO995, a follow-on TRK inhibitor also licensed to Bayer and in Phase I/II for patients with TRK fusion cancers; LOXO292, an oral RET inhibitor in Phase I/II for RET fusion-negative non–small cell lung cancer, medullary thyroid cancer, and other tumors with increased RET activity; and LOXO305, an oral BTK in Phase I/II for B-cell cancers including certain leukemias and lymphomas. The deal is the second major M&A announced in just the first week of the new year: BMS is buying Celgene for $74bn plus CVRs in an acquisition revealed just days prior to Lilly’s news. Investment Banks/Advisors: Deutsche Bank AG (Eli Lilly & Co.;) Goldman Sachs & Co. (Loxo Oncology Inc.)

ALLIANCES
ABBVIE INC. COHERUS BIOSCIENCES INC. Coherus BioSciences Inc. and AbbVie Inc. have settled global patent litigation surrounding CHS1420 (adalimumab/steel-1, Coherus’ proposed biosimilar of AbbVie’s Humira). Under the settlement, Coherus gets worldwide non-exclusive rights to AbbVie’s Humira-related intellectual property. In the US, Coherus’ license commences on December 15, 2023 and it will pay AbbVie royalties. Coherus anticipates filing the BLA in late 2019 and plans to explore options and strategies for ex-US commercialization of CHS1420. AbbVie has penned similar agreements, most recently with Momenta in November 2018. (Jan.)

ABBVIE INC. TIZONA THERAPEUTICS INC. Tizana Therapeutics Inc. granted AbbVie Inc. the option to license exclusive global rights to develop and commercialize CD39-targeted therapeutics including TTX030 for cancer. (Jan.) AbbVie paid Tizzana $105mm up front and make an equity investment in the company. Tizana will conduct clinical trials through the end of Phase lb, after which point AbbVie can opt to take over. Tizana retains the option to co-develop and co-promote in the US. AbbVie could also shell out development and commercial milestones, plus tiered sales royalties. TTX030 is a preclinical monoclonal antibody that inhibits the activity of CD39 and catalyzes the conversion of immune stimulatory extracellular ATP to immune suppressive adenosine in the tumor microenvironment. It also prevents ATP degradation, thus preserving its ability to stimulate dendritic and myeloid-derived cells responsible for innate immunity and immune cell priming necessary for adaptive immunity. An IND application for TTX030 was accepted by the FDA.

ACER THERAPEUTICS INC. SANOFI Sanofi granted Acer Therapeutics Inc. exclusive global rights to osanetan, a non-peptide tachykinin NK3 receptor antagonist. (Jan.) Sanofi originally advanced the candidate into Phase II trials for schizophrenia, but discontinued development in 2003. Acer now takes over and intends to study it for undisclosed neuroendocrine-related disorders. Acer is developing therapies for rare diseases with unmet need. Its pipeline includes late-stage Edsivo (clippedrol) for vascular Ehlers-Danlos syndrome, and ACER001 for maple syrup urine diseases and urea cycle disorders.

ADAPTIVE BIOTECHNOLOGIES CORP. ROCHE Genentech Inc. Adaptive Biotechnologies Corp. licensed Roche’s Genentech Inc. global rights to develop, manufacture, and sell neoantigen-directed T-cell therapies for multiple cancers. (Jan.) Genentech pays $300mm up front; over $2bn in development, regulatory, and commercial milestones; and sales royalties. The alliance will take advantage of Adaptive’s discovery and immune profiling platform TruTCR to identify TCR targets, initially starting with a library that has been screened against thousands of known cancer antigens. Neoantigens are encoded with tumor-specific genes, enabling such T-cell-directed therapy to be personalized to the patient. Adapt will be in charge of worldwide screening, which will take place during the manufacturing process for each individual patient.

ALEXION PHARMACEUTICALS INC. FORTRESS BIOTECH INC. Caelum Biosciences Inc. Alexion Pharmaceuticals Inc. and Caelum Biosciences Inc. agreed to collaborate on the development of Caelum’s CAEL101 (mAb 11-1F4) for amyloid light chain (AL) amyloidosis, a rare systemic disorder that causes the buildup of misfolded immunoglobulin light chain protein in tissues. (Jan.) CAEL101, a chimeric fibril-reactive monoclonal antibody, is designed to improve organ function by reducing or eliminating amyloid deposits, which, if untreated, may result in progressive damage to the organs, particularly the heart and kidneys. Currently in Phase I, CAEL101 was originally licensed to Caelum in 2017 from Columbia University, which had previously received FDA orphan drug status for the mAb as both a radio-imaging agent in amyloidosis and as a potential therapy in the AL amyloidosis indication. Alexion will pay $30mm up front for a 19.9% equity interest in Caelum and $30mm in milestone-dependent development fund-
ioring (includes $55m upon equivalence of the clinical supply of CAEL101; $50mm upon first patient dosing in a Phase II trial; and $155m upon the enrollment of 50% of patients in a Phase II clinical trial). The partners will jointly design the ongoing development program for CAEL101, with Caelum responsible for manufacturing and conducting development through the end of Phase II, at which point Alexion has the exclusive option to acquire the rest of the company for a price between $150-200mm, depending on BLA approval timing for CAEL101. Should it exercise the purchase option, Alexion could additionally provide up to $325mm in regulatory- and commercialization-based earn-out payments related to CAEL101 ($50-75mm upon BLA approval; $25mm for sales (within a calendar year) exceeding $250mm; $50mm for sales exceeding $500mm; $75mm for sales exceeding $750mm; and $100mm for sales exceeding $1bn).

Fortress Biotech Inc. founded Caelum in February 2017 and held a majority stake, but following Alexion’s current equity investment, Fortress’ ownership is now reduced to approximately 40%. (Fortress is eligible to receive about 43% of the proceeds if Alexion exercises the option.)

ALLERGAN PLC

IRONWOOD PHARMACEUTICALS INC.

MYLAN NV

Mylan Pharmaceuticals Inc.

Ironwood Pharmaceuticals Inc. and Allergan PLC have settled patent litigation with Mylan Pharmaceuticals Inc. surrounding Mylan’s abbreviated new drug applications for generic Linzess (linaclotide). Under terms of the settlement, Mylan can begin marketing in the US linaclotide 145mg and 290mg doses starting February 5, 2030, and 72mcg strength August 5, 2030, both subject to FDA approval. Linzess is indicated for irritable bowel syndrome and constipation. Last year Ironwood and Allergan signed similar Linzess patent lit deals with Sun Pharmaceutical (February) and Aurobindo (May). (Jan.)

ALLERGAN PLC

KOWA CO. LTD.

Kowa Pharmaceuticals America Inc.

Allergan PLC granted Kowa Pharmaceuticals America Inc. non-exclusive rights to co-promote its hypertension drug Bystolic (nebivolol) in the US. (Jan.)

Financial terms were not disclosed. Kowa will promote Bystolic to cardiologists and certain primary care healthcare providers using its 300 cardiometabolic sales specialists. Bystolic is a beta blocker designed to lower blood pressure in patients with hypertension. Kowa will sell the product with its own cholesterol-lowering therapeutic Livala (pitavastatin) tablets.

AMGEN INC.

TEVA PHARMACEUTICAL INDUSTRIES LTD.

Teva Pharmaceutical Industries Ltd. settled ongoing patent litigation with Amgen Inc. in which Teva agreed to stop selling its generic cinacalcet HCL (brand name Sensipar) until its license date in mid 2021. As part of the agreement Teva will also pay Amgen an undisclosed amount. Cinacalcet is a calcium-sensing receptor agonist for hyperparathyroidism in adults with chronic kidney disease who are on dialysis. (Jan.)

ASCLETIS PHARMA INC.

JIANGSU ALPHAMAB BIOPHARMACEUTICALS CO. LTD.

Alphamab Co. Ltd. licensed Ascleptis Pharma Inc. exclusive rights to develop and commercialize KNO35 (renamed ASC22) in China, Hong Kong, Macao, and Taiwan for viral diseases, including hepatitis B. (Jan.)

Alphamab received money up front and is eligible for development and commercial milestones, plus tiered sales royalties from the mid-teens to around twenty percent. (Strategic Transactions assumes 14-20%). Alphamab will manufacture ASC22 for Ascletis. For ASC22 in viral indications worldwide outside Greater China, Ascletis is eligible to share certain up-front, milestone, and royalty payments, subject to the development and regulatory status of ASC22 in the licensed territory. ASC22 is a programmed cell death ligand-1 (PD-L1) monoclonal antibody that has been tested in over 500 patients in various clinical trials in the US, China, and Japan. The subcutaneous route of administration for ASC22 offers a differentiated approach to treating HBV. Ascletis expects to begin Phase II trials in 2019. The compound is also in Phase II for cholangiocarcinoma and Phase III for solid tumors. Alphamab says it anticipates a broader and long-term partnership with Ascleptis in viral and liver diseases in the future.

BIODRUGS INC.

C4 THERAPEUTICS INC.

Biogen Inc. and C4 Therapeutics Inc. are teaming up to identify and develop therapeutics for neurological conditions including Alzheimer’s and Parkinson’s diseases based on C4’s protein degradation platform. (Jan.)

To the collaboration, C4 will contribute its research services and capabilities in targeted protein degradation, while Biogen provides its expertise in the neuroscience space and drug development. Both parties will perform research activities and Biogen will be responsible for development and commercialization activities. C4 will receive up to $415mm in up-front and milestone payments, plus sales royalties. C4’s technology uses the innate mechanisms of cells to eliminate specific disease-causing proteins. Concurrent with the agreement with Biogen, C4 Therapeutics penned a deal with Roche focused on developing new cancer therapies using C4’s technology.

BIODRUGS INC.

SKYHAWK THERAPEUTICS INC.

Biogen Inc. and Skyhawk Therapeutics Inc. are teaming up to develop small-molecule therapeutics for neurological diseases including multiple sclerosis and spinal muscular atrophy using the SkySTAR platform. (Jan.)

Biogen will have the option to license exclusive global rights to develop and commercialize resulting therapeutics. Skyhawk received $74mm up front and is eligible for milestones and royalties. SkySTAR stands for Skyhawk Small molecule Therapeutics for Alternative splicing RNA. The platform is used to develop candidates that can correct an RNA splicing defect (exon skipping), which results in RNA mutations that cause diseases including cancer and neurological conditions. Concurrent with the deal, Biogen signed a potential $415mm neurology deal with C4 Therapeutics.

BIOHARMONY THERAPEUTICS INC.

BOEHRINGER INGELHEIM GMBH

Bioharmony Therapeutics Inc. and Boehringer Ingelheim GMBH agreed to collaborate on the development of bacteriophage lysins for the treatment of multidrug-resistant (MDR) Acinetobacter infections. (Jan.)

The initial discoveries were licensed by Bioharmony from the lab of Vincent Fischetti, PhD, at Rockefeller University. The infections are a common cause of hospital-acquired pneumonia and life-threatening blood or wound infections, with around 9% of all bacterial infections in intensive care worldwide caused by them. As a new antimicrobial class, lysins are bacteriophage-derived enzymes that cleave the essential bonds in the bacterial cell wall to rapidly kill the target bacteria. Infectious disease is an area outside of Bi’s core focus and will be taken on by its Research Beyond Borders department.

BIOTIME INC.

ORBIT BIOMEDICAL LTD.

In an exclusive twelve-month deal, BioTime Inc. and start-up Orbit Biomedical Ltd. are collaborating on the delivery of BioTime’s dry age-related macular degeneration candidate using Orbit’s technology. (Jan.)

BioTime’s OpRegen is in Phase I/II for dry-AMD. The firms will investigate the safety and utility of Orbit Biomedical’s injection technology to deliver BioTime’s OpRegen stem cell therapy. Orbit’s technology provides an alternative to accessing the sub-retinal space via vitrectomy, which involves piercing the retina to remove the vitreous. Instead, the injection system can precisely and consistently deliver
therapeutics to the sub-retinal space via a suprachoroidal route. Under the agreement, BioTime has the option to license exclusive rights for the commercial use of the device with OpRegen.

BOEHRINGER INGELHEIM GMBH SCIENCE 37 INC.

Boehringer Ingelheim GMBH licensed rights to Science 37 Inc.’s NORA (Network Oriented Research Assistant) proprietary software platform. (Jan.)
The technology allows patients to remotely participate in clinical trials, thereby increasing diversity, efficiency and speed, and decreasing the patient burden. The remote clinical trial model (known as the Metasite) helps researchers engage directly with trial subjects from screening and recruitment to telemedicine-based patient care to data lock. Science 37 will advise BI on study design, protocol development, and regulatory strategy for remote clinical trials.

BOEHRINGER INGELHEIM GMBH VANDERBILT UNIVERSITY

Vanderbilt Center for Neuroscience Drug Discovery

Boehringer Ingelheim GMBH agreed to partner with Vanderbilt Center for Neuroscience Drug Discovery to develop and commercialize novel small molecules that target distinct G-protein coupled receptors (GPCRs). The two companies already have an existing partnership in oncology. (Jan.)
Maladaptive brain circuits can cause memory, concentration, and decision-making difficulties along with social withdrawal, lack of motivation, and the inability to experience pleasure. GPCRs are known to have specific roles in the regulation and modulation of brain circuit functions and therefore show promise to relieve some of these symptoms. The focus of the collaboration will be on schizophrenia and other major psychiatric disorders. Just last month BI teamed up with Domain Therapeutics to discover GPCR drugs. Using GPCR to treat disease is beginning to gain traction. Last year, startup Escient Pharmaceuticals launched and raised $40mm in its Series A round to advance first-in-class GPCR-targeted drugs for neuro-immuno-inflammatory and auto-reactive diseases.

CANBRIDGE LIFE SCIENCES LTD.

GC PHARMA

GC Pharma (formerly known as Green Cross Corp.) granted CANbridge Life Sciences Ltd., exclusive Chinese commercialization rights to its Hunterase (GC1111; iduronate-2-sulfatase (IDS)) for Hunter syndrome (mucopolysaccharidosis Type II; MPS II). (Jan.)
An injectable human IDS enzyme replacement therapy, Hunterase was approved in Korea in 2012 for MPS II—a rare inherited lysosomal storage disease. It is currently sold in more than ten countries worldwide. CANbridge plans to file for approval in China in 2H 2019 and anticipates soon beginning a Phase II trial in the US, where the therapy received FDA orphan drug designation in 2013. The deal boosts CANbridge’s rare genetic disease pipeline and gives GC Pharma a partner experienced in the Chinese market.

CELGENE CORP.

KYN THERAPEUTICS

Kyn Therapeutics will grant Celgene Corp. exclusive options to license two of its preclinical immuno-oncology projects. (Jan.)
The deal comes just weeks after Celgene announced that it is being acquired by BMS for $74bn. (Kyn tells Informa that the acquisition did not play a role in its decision to pair up with Celgene.) Under terms of the deal, Kyn will develop its aryl hydrocarbon receptor (AHR) antagonist program and a kynurenine-degrading enzyme program through Phase Ib, at which time Celgene can exercise its option to fund and lead global development and commercialization. Celgene paid $80mm up front and made an equity investment in Kyn; it will also hand over significant development, regulatory, and commercialization milestones, plus tiered royalties. The optioned projects are attractive for patients who do not fully respond to checkpoint inhibitor regimens due to the fact that both targets (AHR and kynurenine) are associated with immunosuppression through a range of cellular metabolic mechanisms that modulate innate and adaptive immunity. Concurrent with the Kyn deal, Celgene also announced that it has optioned rights to license IL12- and CD40L-based cell therapies developed by Obsidian Therapeutics.

CELGENE CORP.

OBSDIAN THERAPEUTICS INC.

Cell therapy developer Obsidian Therapeutics Inc. has found its first major partner through a new deal with Celgene Corp., surrounding Obsidian’s Destabilizing Domains (DD) technology. (Jan.)
Destabilizing Domains are fully human protein domains that allow for pharmacologic regulation of transduced gene expression. The technology (in-licensed from Stanford University) allows for the design of tunable cell and gene therapies with controllable functions. During the multi-year deal, Celgene and Obsidian will focus on utilizing DD for controlled expression of the immunomodulatory factors IL12 and CD40L. Celgene holds an exclusive option to license global rights to resulting cancer therapies incorporating regulated IL12 or CD40L. It pays money up front, including an equity investment in Obsidian, and will also be responsible for milestones and royalties. Celgene announced the deal on the same day it revealed details of a tie-up with Kyn Therapeutics (Celgene gets options to two of Kyn’s immuno-oncology projects) and just a couple of weeks after BMS announced that it would pay $74bn to buy Celgene.

CELGENE CORP.

TRIPHASE ACCELERATOR CORP.

Building on a successful relationship that began in 2012, Triphase Accelerator Corp. and Celgene Corp. have entered a new deal surrounding the development of Triphase’s leukemia candidate TRPH395. (Jan.)
Under the current collaboration, Celgene paid $40mm up front for an option to acquire TRPH395, a WDR5 inhibitor in preclinical studies for acute myeloid leukemia. If it exercises the option, Celgene could pay up to $940mm in development, regulatory, and sales milestones, plus royalties. In 2012, Celgene gained right of first refusal on the first three candidates to be development by Triphase, including Phase I/II proteasome inhibitor marizomib for multiple myeloma and glioblastoma, which Celgene licensed exclusively in 2016. From that deal, the pair are also working on Triphase’s CD22 antibody-drug conjugate TRPH22 for non-Hodgkin lymphoma, according to the company’s pipeline. Announcement of the new deal comes as Celgene is in the process of being acquired by BMS (which is paying a whopping $74bn). The acquisition has not slowed Celgene’s deal-making endeavors: since the M&A was announced, it signed deals with Obsidian for cell therapies, and also paid $80mm up front and committed significant royalties to new immuno-oncology partner Kyn Therapeutics.

CODIAK BIOSCIENCES INC.

JAZZ PHARMACEUTICALS PLC

Codiak BioSciences Inc. granted Jazz Pharmaceuticals PLC exclusive global rights to develop, manufacture, and sell candidates directed at five targets that will be developed using Codiak’s engEx exosome platform. (Jan.)
The deal will focus on oncogenes that are well validated in solid and blood cancers but are as-yet undruggable with current treatments including STAT3 and NRAS. Jazz pays $56mm up front; $20mm in preclinical milestones for all five projects; $200mm per target in milestones for development, regulatory, and sales achievements; and royalties ranging from the mid-single digit to high-teens (Strategic Transactions estimates 4-19%). Codiak will carry out preclinical and early development (through Phase I/II POC studies) before turning over the reins to Jazz and retains an option for co-commercialization and cost-sharing in the US and Canada for up to two resulting products. The engEx precision engineering platform allows for the incorporation of a range of drug classes (small molecules, proteins, peptides, etc.) onto the surface or in the lumen of therapeutic exosomes.
CytoReason and Pfizer Inc. have signed a drug discovery and development collaboration. (Jan.)

The alliance will capitalize on CytoReason's platform based on cell-centered models of the immune system. The technology uses data and machine-learning to reconstruct cellular information from bulk tissue, train an immune-specific NLP engine, and integrate multi-omics data. Pfizer will pay CytoReason up to low-double-digit millions (Strategic Transactions assumes up to $29mm) in the form of technology access fees, research funding, and certain success-based milestones.

Specific disease areas to be examined in the collaboration were not disclosed.

Denali Therapeutics Inc.
Siron Biotech GMBH and Denali Therapeutics Inc. have agreed to jointly develop adeno-associated virus (AAV) vectors to create CNS gene therapies capable of crossing the blood-brain barrier (BBB). AAV vectors are considered a promising gene delivery system. (Jan.)

The agreement covers applications in neurodegenerative diseases, including Parkinson’s and Alzheimer’s diseases and ALS. Siron contributes expertise from its partner under a 2018 deal, the Heidelberg Hospital, where the work of Dirk Grimm, MD, PhD, in the field of AAV biology and application involves the engineering and high-throughput in vivo screening of AAV capsid libraries. Denali’s own large-molecule delivery technologies (Antibody Transport Vehicle and Enzyme Transport Vehicle) are designed to engage BBB transport receptors and enhance delivery of therapeutic proteins to the brain. The companies will combine their platforms to create next-generation AAV vectors, with the goal of developing new and modified AAV capsids that offer a safe profile, improved specificity, high efficiency delivery to the brain, and increased availability within the brain. Denali will pay up-front and contingent milestone payments, fund development costs, and provide low-to-medium single-digit royalties (Strategic Transactions estimates 1-6%) on net sales of resulting products or therapies. The deal enables Denali to potentially boost its protein therapeutics in development for neurodegenerative disorders. The company’s pipeline already includes both small- and large-molecule candidates engineered for brain delivery.

Fibrocor Therapeutics LP
Fibrocor Therapeutics LP licensed Galapagos NV worldwide rights to develop and commercialize a small-molecule inhibitor aimed at idiopathic pulmonary fibrosis (IPF) and other indications. (Jan.)

Galapagos will pay Fibrocor money up front, milestones, and sales royalties. Fibrocor currently has the program in
lead optimization for treating fibrotic diseases of the lung and other organs. Galapagos will take over further development. Fibrocor was created in early 2017 by Evotec AG to develop therapies that can prevent, slow, and even reverse the course of fibrosis.

GILEAD SCIENCES INC.

Yuhan Corp.

Yuhan Corp. granted Gilead Sciences Inc. global rights (excluding the Republic of Korea) to co-develop and commercialize small molecules against two undisclosed targets for advanced fibrosis due to non-alcoholic steatohepatitis (NASH). (Jan.) The partners will jointly perform preclinical work, after which Gilead will take over clinical trials and commercialization in its territories. Yuhan gets $155mm upfront and up to $770mm in development and sales milestones, plus royalties. The deal builds on an existing commercial relationship between the pair, focused on Gilead’s products in Korea, and helps build Gilead’s NASH pipeline further. The company currently has one candidate for the disease in Phase III (selonsertib, an ASK1 inhibitor) and two others in Phase II.

GRIFOLS SA

Rigel Pharmaceuticals Inc.

Rigel Pharmaceuticals Inc. granted Grifols SA exclusive rights to commercialize fostamatinib for all potential indications including chronic immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA), and IgA nephropathy (IgAN) in Europe and Turkey. (Jan.) Fostamatinib, marketed in the US as Tov公is, is the only approved SYK inhibitor for thrombocytopenia in adults with chronic immune thrombocytopenia who have not responded successfully to prior treatments. The EMA accepted Rigel’s marketing authorization application for fostamatinib in October 2018, and Rigel expects a decision by the end of 2019. Grifols paid $350mm upfront and could hand over up to $297.5mm in regulatory milestones and sales payments, plus tiered double-digit royalties spanning up to 30%. If the drug has not been approved in Europe by the deal’s second anniversary, the deal can terminate and Grifols will be eligible for a $25mm payment. The licensing is Rigel’s second for fostamatinib in less than a year. In late 2018, Kissei gained exclusive marketing rights in Japan, China, Taiwan, and the Republic of Korea.

H. LUNDBECK AS

Numerate Inc.

H. Lundbeck AS and Numerate Inc. have agreed to collaborate on the discovery of CNS therapeutics using Numerate’s artificial intelligence (AI) drug design capabilities. (Jan.)

In the multi-target research collaboration, Numerate will apply its data-driven AI capabilities (created by a team of computer scientists, data scientists, medicinal chemists, and biologists) to identify candidates for CNS diseases, including depression, psychosis, seizure, and neurodegenerative disorders. In exchange, Lundbeck contributes its discovery and development expertise in neurological disease therapeutics and will provide up-front money, R&D funding, milestone payments, and royalties. Applying AI algorithms that use internal modeling capabilities of real biology, Numerate’s D4 platform is designed to predict a drug’s ADMET (absorption, distribution, metabolism, excretion and toxicity) to identify potential liabilities earlier in the discovery process to increase both speed and success. Numerate’s approach is intended to overcome challenging small-molecule drug design, including identification of chemistries for previously undruggable CNS targets.

HEMOSHEAR THERAPEUTICS LLC

HORIZON PHARMA PLC

Horizon Pharma PLC and HemoShear Therapeutics LLC are teaming up to identify and develop gout therapies. (Jan.) The deal will capitalize on HemoShear’s REVEAL-Tx disease modeling platform that can replicate the biology of diseases and help researchers select relevant drug candidates to develop. Horizon will receive exclusive rights to the platform to use in discovering gout therapies. In exchange, HemoShear will receive undisclosed up-front payments and funding for R&D. Horizon gets rights to any resulting therapies and could shell out over $500mm in development and commercial milestones, plus sales royalties. Gout is a painful condition caused by excess uric acid in the body that can lead to significant joint damage. This is HemoShear’s second metabolic disease alliance in as many months. It recently teamed up with SmartZyme’s new spin-off Carnot Biosciences to develop protein-based therapies for rare metabolic diseases.

JOHNSON & JOHNSON

Janssen Pharmaceuticals Inc.

MeiraGTx Holdings PLC

MeiraGTx Holdings PLC and Janssen Pharmaceuticals Inc. are teaming up in the development and commercialization of gene therapies for inherited retinal diseases (IRD). (Jan.)

Included in the agreement are MeiraGTx’s Phase I/II AAV-CNGB3 for achromatopsia and AAV-RPGR X-linked retinitis pigmentosa, and preclinical AAV-CNGA3 for achromatopsia. Both firms will collaborate in clinical development, and Janssen gets worldwide exclusive rights to the programs. Janssen will pay $100mm upfront in cash and could shell out up to another $340mm in development and sales milestones, plus up to 20% sales royalties. Janssen will fund all costs associated with clinical development and commercialization. The agreement is Johnson & Johnson’s largest in the gene therapy space to date. MeiraGTx and Janssen have also penned a research collaboration to develop a pipeline gene therapies for IRDs, with Janssen funding a significant portion of the costs. Janssen has the exclusive option to license those programs when the IND is cleared by the FDA. Should it opt-in it will pay for development and commercial activities. MeiraGTx would receive an opt-in payment, development milestones, and royalties in the high-teens (17-19%). The firms also plan to collaborate on the development of AAV gene therapy manufacturing technology and will share any costs. Just three months ago, the companies penned an agreement involving the use of MeiraGTx’s riboswitch technology to engineer regulatable gene therapies.

KNIGHT THERAPEUTICS INC.

PUMA BIOTECHNOLOGY INC.

Puma Biotechnology Inc. granted Knight Therapeutics Inc. exclusive rights to commercialize the breast cancer drug Nerlynx (neratinib) in Canada. (Jan.) Puma is eligible for up-front and milestone payments totaling up to $72mm, plus double-digit royalties. The company already markets Nerlynx in the US and filed a new drug submission with Health Canada in July 2018 for early-stage HER2-overexpressed/amplified breast cancer following adjuvant therapy with trastuzumab. Knight is responsible for commercialization and any future regulatory filings in its territory, allowing Puma to maintain its focus on the US market.

MERSANA THERAPEUTICS INC.

SYNAFFIX BV

SynAffix BV granted Mersana Therapeutics Inc. nonexclusive rights to use its GlycoConnect antibody-drug conjugate (ADC) platform in its oncology drug development activities. (Jan.) The total potential deal value could hit $295mm, including an up-front payment and milestones, plus sales royalties. GlycoConnect uses proprietary enzymes and metal-free click conjugation to attach ADC payloads to the native glycans of any antibody. Mersana will apply the technology to one of its ADC candidates and has the option to extend the license to cover additional programs. It is responsible for R&D, manufacturing, and commercialization of resulting therapies. The deal stems from an existing research collaboration between the partners.
NEUROCRINE BIOSCIENCES INC.
Voyager Therapeutics Inc. will collaborate on the development of up to four Voyager neurological disease candidates. The deal includes two adeno-associated virus (AAV) potential gene therapies—VYAADC, a DOPA decarboxylase stimulant in Phase II for Parkinson’s disease (PD) and pre-clinical VYFXN01, a frataxin agonist for Friedreich’s ataxia (FA)—plus two yet-to-be-determined discovery programs. (Jan.)

Neurocrine funds development costs for all four programs and pays $165mm up front ($155mm in cash and $50mm in Voyager equity (4.2mm Voyager shares at $11.96, a 43% premium); up to $625mm in development milestones (up to $70mm for VYAADC, up to $195mm for VYFXN01, and up to $350mm apiece for the two discovery programs); up to $1.1bn in commercialization milestones (up to $275mm per project); and royalties on sales. The royalties range from the mid-teens to thirty (14-30%) in the US and the low-teens to twenty (13-20%) outside the US for VYAADC; the low-teens to high-teens (13-19%) in the US and high-single-digits to mid-teens (7-16%) outside the US, and high-single-digits to mid-teens (7-13%) outside the US for each discovery program. For VYAADC, Neurocrine funds the Phase II/III pivotal study in PD. After results of the ongoing Phase II RESTORE-1 trial, Voyager has the option to co-commercialize VYAADC with Neurocrine in the US under a 50/50 cost- and profit-sharing arrangement and receive milestones and royalties based on ex-US sales, or grant Neurocrine exclusive worldwide commercialization rights in exchange for milestones and royalties based on global sales. For VYFXN01, Neurocrine funds development through the Phase I trial, after which Voyager has the option to co-commercialize VYFXN01 in the US under a 60/40 cost- and profit-sharing arrangement, or grant Neurocrine full US commercialization rights in exchange for milestone payments and royalties on US sales. (Sanofi Genzyme, under a 2015 agreement, retains an option for ex-US rights to VYFXN01 following results of the Phase I trial). For the two discovery programs, Neurocrine will pay Voyager milestones and royalties based on global sales. The deal extends Voyager’s cash runway into 2022 and the addition of its neurological disease gene therapy programs boost Neurocrine’s existing neurology pipeline, which includes opicapone (Phase III) for PD and valbenazine (Phase II) for Tourette syndrome. Investment Banks/Advisors: Centerview Partners LLC (Neurocrine Biosciences Inc.)

NOVARTIS AG
OCULIS
Oculis in-licensed Novartis AG’s LME636 compound, indicated for inflammatory conditions of the anterior segment of the eye. (Jan.)

LME636, which Oculis will rename OC502, is a topically delivered anti-TNF alpha antibody in Phase II for dry eye and uveitis. Efficacy and safety of OC502 have been evaluated in three clinical trials. Novartis eye care division Alcon gained the compound through its 2009 acquisition of ESBAtech AG, and previously partnered it with Apexigen. (Novartis spun off the device assets of Alcon as a separate company mid last year but held onto the pharma business.) Oculis plans to develop OC502 with support from separate funding raised in a concurrent Series B financing round extension. (Oculis originally raised $20.3mm in early 2018, and the additional funding brings the total round to $36mm.) OC502 joins Oculis’ ophthalmic pipeline of topical candidates, including OC501 (formerly OC18), currently in Phase II for diabetic macular edema (with plans for advancing in potential front-of-the-eye indications).

OCULAR THERAPEUTIX INC.
Purdue Pharma LP and Ocular Therapeutics Inc. are partnering to develop a sustained-release delivery alternative for Purdue’s pain candidates. (Jan.)

Ocular will apply its bioresorbable hydrogel-based technology to undisclosed Purdue non-opioid new chemical entities to determine the platform’s effectiveness in delivering pain therapeutics. Ocular is responsible for initiating formulation testing, which it aims to progress to a point of efficacy assessment. Ocular’s hydrogel platform takes drugs known to be safe and efficacious when formulated as drops or injections and creates dosage forms capable of delivering sustained therapeutic levels of the drug to targeted ocular tissues. The platform aims to reduce dosing frequency, improve patient compliance, and provide better drug safety and efficacy. Ocular has previously applied the technology solely to conditions of the eye; the current deal will evaluate it for the first time in a non-ophthalmic indication.

PURETECH HEALTH PLC
Alivio Therapeutics
Purdue Pharma LP and PureTech Health PLC’s Alivio Therapeutics will collaborate on the clinical development of Alivio’s ALV107 non-opioid interstitial cystitis/bladder pain syndrome (IC/BPS) candidate. (Jan.)

Purdue has the option to collaborate on a set number of additional compounds that use Alivio’s inflammation-targeting technology, as well as an option to invest in Alivio’s next equity financing. Purdue will provide $14.75mm up front (including near-term license exercise payments), up to an additional $260mm in R&D milestones, plus royalties on product sales. An ascorbyl palmitate hydrogel with encapsulated lidocaine, ALV107 incorporates a patented hydrogel technology, which was developed by company co-founders Robert Langer, ScD (of MIT) and Jeff Karp, PhD (of Brigham & Women’s Hospital), and licensed to Alivio from their respective institutions. The hydrogel material is designed to adhere to and deliver an active drug to inflamed tissue with an ability to control drug release depending on the degree of inflammation present. Preclinical data presented for ALV107 in July 2017 demonstrated durable pain control during a 24-hour study period (lasting at least 12 times longer than lidocaine at a comparable dose) and supports the candidate as a potential IC/BPS treatment. (Alivio is also evaluating this approach in multiple acute and chronic inflammatory disorders, including pouchitis and inflammatory bowel disease.) The deal supports Purdue’s mission to distance itself from opioid pain drugs.

SCPHARMACEUTICALS INC.
West Pharmaceutical Services Inc. and ScPharmaceuticals Inc. and West Pharmaceutical Services Inc. are teaming up to incorporate West’s SmartDose drug delivery system with scPharma’s Furoscix. (Jan.)

Furoscix is scPharma’s lead program for treating edema in patients with heart failure. Recently completed preliminary feasibility studies showed that the West SmartDose system could successfully deliver Furoscix. That testing included drug stability in the pre-filled cartridge, drug compatibility, and overall performance. SmartDose is a wearable patch injector that enables hands-free drug delivery. The first combination product that incorporates the SmartDose has been approved by the FDA. In October 2018, scPharma announced that the FDA asked that it conduct additional human factors studies and a dose delivery validation study with Furoscix. The company plans to complete those studies required to refile Furoscix by the end of 2019. ScPharma seeks to expedite the advancement of a next-generation on-body delivery system with a pre-filled cartridge and anticipates filing the NDA in 2020.

FINANCINGS
ACCELERON PHARMA INC.
Acceleron Pharma Inc. netted $216.2mm in a follow-on public offering of 5.35mm common shares at $42 each. The company plans to use the proceeds for clinical trials
of its pulmonary hypertension and neuromuscular candidates and for potential partnerships. (Jan.)
Investment Banks/Advisors: Citigroup Inc.; JP Morgan & Co.; SVB Financial Group; UBS Investment Bank

AIMMUNE THERAPEUTICS INC.
Aimmune Therapeutics Inc. (immuno-therapies for allergies) entered a $170mm loan agreement with an affiliate of KKR, the proceeds of which will fully fund commercialization of the company’s peanut allergy immunotherapeutic AR101. Proceeds will also go towards continued pipeline development, including Phase II work on AR201 for egg allergy. The company drew down $40mm immediately. A further draw of $85mm could be released upon FDA approval of AR101, and the remaining $40mm will be available in 2020 under certain conditions. (Jan.)

ALECTOR INC.
Alector Inc. (immuno-neurology antibody therapeutics) filed for an initial public offering. (Jan.)
Investment Banks/Advisors: Bank of America Merrill Lynch; Barclays Bank PLC; Cowen & Co. LLC; Morgan Stanley & Co.

ALNYLAM PHARMACEUTICALS INC.
Alnylam Pharmaceuticals Inc. netted $382.3mm through the follow-on public offering of 5mm common shares at $77.50 each. The company will use the proceeds for ongoing manufacturing and US and EU commercial activities for its Onpattro (patisiran) lipid complex injection for treating adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis; to launch the product in additional countries worldwide; for global launches of givosiran (for acute hepatic porphyria), lumasiran (for global launches of givosiran for acute hepatic porphyria, lumasiran for primary hyperoxaluria Type 1, and vutrisiran for ATTR amyloidosis; and for R&D and commercialization of new RNAi therapeutics. (Jan.)
Investment Banks/Advisors: Barclays Bank PLC

ALPINE IMMUNE SCIENCES INC.
Alpine Immune Sciences Inc. (multifunctional immunotherapies for cancer and autoimmun-inflammatory diseases) grossed $25mm through the private placement of 4.7mm common shares at $5.37 (an 8% premium) to an investor syndicate led by Decheng Capital and including existing investors OrbiMed Advisors, Frazier Healthcare Partners, Alpine BioVentures, and BVF Partners. Investors also received five-year warrants to purchase 1.8mm shares at $12.74, Piper Jaffray was the placement agent. Proceeds will support continued development of ALPN101 (preclinical for psoriatic arthritis and graft-versus-host disease) and ALPN202 (preclinical for cancer). (Jan.)
Investment Banks/Advisors: Piper Jaffray & Co.

ANCHIANO THERAPEUTICS INC.
Anchiano Therapeutics Inc. (developing gene therapies for cancer) filed for an initial public offering of its American Depositary Shares in the US. The company is already listed on the Tel Aviv Stock Exchange. (Jan.)
Investment Banks/Advisors: Ladenburg Thalmann & Co. Inc.; Oppenheimer & Co. Inc.

BELLEROPHON THERAPEUTICS INC.
Bellerophon Therapeutics Inc. (cardiopulmonary diseases) netted $6.5mm through the follow-on public offering of 10mm common shares at $0.70 each. (Jan.)
Investment Banks/Advisors: HC Wainwright & Co.

COHERUS BIOSCIENCES INC.
Coherus BioSciences Inc. entered into a $75mm senior secured credit facility with Healthcare Royalty Partners. The facility matures on February 7, 2025 and bears interest at a rate of 3-month LIBOR plus 7% per year (also subject to a 4% final payment premium on the entire principal amount funded). Funds will be used to accelerate and enhance the manufacturing and sale of FDA-approved biosimilar UDENYCA (pegfilgrastim-cbqv), a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. (Jan.)

KALEIDO BIOSCIENCES
Kaleido Biosciences Inc. filed for its initial public offering on the Nasdaq. (Jan.)

MIRATI THERAPEUTICS INC.
Mirati Therapeutics Inc. (target oncology treatments) netted $188mm through the public sale of 1.85mm common shares (including the overallotment) at $62. The company will use the money to support ongoing clinical trials of sitravatinib for lung, bladder, renal, liver, gastric, ovarian, and other solid tumors; MRTX849, entering Phase I for non-small cell lung and colorectal cancers; and for preclinical projects. (Jan.)
Investment Banks/Advisors: Barclays Bank PLC; Citigroup Inc.; Cowen & Co. LLC; Credit Suisse First Boston; JP Morgan Chase & Co.

POSEIDA THERAPEUTICS INC.
CART therapy developer Poseida Therapeutics Inc. filed for its initial public offering. (Jan.)
Investment Banks/Advisors: Citigroup Inc.; Credit Suisse Group; Wells Fargo Securities LLC

PTC THERAPEUTICS INC.
PTC Therapeutics Inc. netted $200mm through a public offering of 6.7mm common shares at $30.20. Proceeds are earmarked for continued work on the company’s gene therapy and alternative splicing programs for rare diseases and cancer; gene therapy manufacturing activities; and commercialization of Translarna (ataluren) outside of the US for nonsense mutation Duchenne muscular dystrophy (nmDMD), Emflaza (deflazacort) in the US for DMD, and Tegsedi (inotersen) and Waylivra (volanenorsen) for rare diseases in Latin America and the Caribbean. (Jan.)
Investment Banks/Advisors: RBC Capital Markets

REVANCE THERAPEUTICS INC.
Revance Therapeutics Inc. netted $94mm through the public offering of 5.9mm shares at $17. The company will use the proceeds to fund clinical trials and R&D expenses. Revance concurrently announced it would present (at an upcoming conference) clinical and non-clinical data for its long-acting neuromodulator RToo2 (daxibotulinumtoxinA) injection, including results from two Phase III pivotal studies for glabellar lines; results of a Phase II dose-escalating study in cervical dystonia; and methodology for a Phase II efficacy and safety trial in upper limb spasticity following stroke or traumatic brain injury. RToo2 utilizes the company’s peptide and formulation technology. (Jan.)
Investment Banks/Advisors: Cowen & Co. LLC; Goldman Sachs & Co.; Guggenheim Partners LLC; Piper Jaffray & Co.

SELECTA BIOSCIENCES INC.
Selecta Biosciences Inc. (developing biologics using its tolerogenic SVP [Synthetic Vaccine Particles] platform) netted $28.2mm via a follow-on public offering of 20mm common shares at $1.50 each. The company plans to use some of the proceeds for ongoing development of lead candidate SEL212, which is in Phase II for severe chronic gout, and for preclinical programs. (Jan.)

STEMLINE THERAPEUTICS INC.
Stemline Therapeutics Inc. (oncology) netted $86.5mm through an upsized public
sale of 10.2mm common shares (including the overallotment) at $9. Funds will support commercialization activities for Elzonris (tagraxofusp; blastic plasmacytoid dendritic cell neoplasm (BPDCN)) and additional development of the drug for chronic myelomonocytic leukemia, myelofibrosis, and other diseases; development of SL801 for solid tumors; and additional R&D and corporate needs. (Jan.)


SUNESIS PHARMACEUTICALS INC.

Sunesis Pharmaceuticals Inc. (developing treatments for solid and blood cancers) netted $18.8mm through concurrent public offerings. The company sold 23mm common shares at $0.50 for net proceeds of $10.8mm, and also issued 17k Series E preferred shares at $500 apiece for net proceeds of $7.99mm. Proceeds will support continued development of vedrutinib, a BTK inhibitor in Phase II for B-cell malignancies, and will also fund ongoing R&D, working capital, and debt amortization. (Jan.)

Investment Banks/Advisors: Oppenheimer & Co. Inc.; Wells Fargo Securities LLC

UROGEN PHARMA LTD.

UroGen Pharma Ltd. (uro-oncology) netted $414mm through the public sale of 3.7mm common shares at $41. Funds will support working capital, development, and commercial infrastructure build-out to support the eventual launch of UGN101 urothelial gel (chemoablation for low-grade bladder cancer) and other pipeline projects. (Jan.)


WAVE LIFE SCIENCES LTD.

Wave Life Sciences Ltd. (nucleic acid therapeutic candidates for genetically defined diseases) netted $141mm in a public offering of 3.95mm shares at $38. The company plans to use the proceeds to fund clinical trials and R&D expenses; growth of its manufacturing capabilities; investments in its synthetic chemistry drug development platform; and building of infrastructure to support the transition to a commercial-stage genetic medicines company. (Jan.)

Investment Banks/Advisors: HC Wainwright & Co.; Jefferies & Co. Inc.; Leerink Partners LLC; Mizuho Bank Ltd.; SunTrust Banks Inc.