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# Pharma Asset Insights

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Bringing science innovation and partnering news to the biopharmaceutical business community

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**Innovation in the pharmaceutical industry** has never been more exciting, and complicated. Disruptive technologies, such as artificial intelligence and digital health tools, and advanced therapeutic modalities including cell and gene therapies and antisense oligonucleotides demand that all health care stakeholders make efforts to move into the next generation of patient care and centricity.

Funding for start-ups has reached an inflection point, with venture capital money flowing into companies at a rapid speed and at record-high amounts, particularly for those located in Europe. In 2013 only three life science venture capital rounds surpassed $100 million; by the first quarter of 2018, those financings have become more of the rule than the exception, as 10 venture rounds worth over $100 million were completed, led by a massive $500 million late-stage funding from Moderna Therapeutics.

Many of these firms have progressed to the IPO stage, where markets have been very favorable over the past couple years. Indeed, 11 biopharma IPOs netted an aggregate $1 billion in Q1 2018, and included a $56 million offering from BioXcel Therapeutics, which is using artificial intelligence to identify the most promising neurological and immune-oncology drug candidates to advance. Overall, companies involved in mining and applying predictive analytics to big datasets have been well funded recently, including BenevolentAI, which closed on a $115 million financing, and Pear Therapeutics, a digital health company that has raised $50 million and signed on Novartis to market its reSET digital therapeutics product for substance abuse.

Big Pharma continues to invest in growth areas that offer chances for commercial significance and success. Gene therapy dealmaking has commanded large deal values from major large and mid-sized companies, while immune-oncology continues to represent an important investment, exemplified by Eli Lilly's $1.6 billion acquisition of Armo BioSciences.

I hope you enjoy this compilation of insights and data-driven analysis from Informa's Pharma intelligence.

**Amanda Micklus**
Principal Analyst, Datamonitor Healthcare, Pharma intelligence

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# Billion Dollar Bets, Health Care Magic

▶ By John Hodgson

- In the past few months, a small group of powerful investment organizations has started to put substantial early investments of more than $100 million and even above $1000 million into companies such as Roivant, Verily and Guardant Health.
- These "unicorn" investments are ploys that aim to create dominant positions in nascent strands of industry.
- The massive upfront funding challenges the thinking of investors who adhere to traditional step-wise funding. Keeping ahead of galloping unicorns is tricky but, tactically, there are things that can be done to prepare for their attack.

The pattern of venture capital investing has changed radically since the 2013. The key change is that the group of investments of over $100 million is now close to becoming the predominant class of venture capital deployed in the life sciences.

## What Is Happening?

There is a clear trend towards the deployment of large amounts of capital in venture investing. In 2013, there were only three life science venture capital rounds worth over $100 million: CAR-T cell immunotherapy play **Juno Therapeutics Inc.** raised $176 million in an A round [See Deal], synthetic biologic specialist **Intrexon Corp.** took $150 million in an F round just before it went public and the still-mysterious mRNA company **Moderna Therapeutics LLC** raised $100 million in a B round. Those three rounds accounted for less than 10% of venture capital (8.5%) raised in 2013, an unspectacular investing year.

In contrast, in the first three months of 2018 alone, there have already been 10 venture rounds over $100 million plus the biggest deal of the year so far: another late venture capital round in February for Moderna, this time worth $500 million. (*See Exhibit 1.*)

However, the proportion of venture capital going into life science in $100 million-plus amounts has increased consistently each year since 2013. (*See Exhibit 2.*) In 2017, the last full year, the fraction was 39.8%. So far 2018 is shaping up to be a stellar year for life science venture capital with over $3.6 billion raised in the first quarter alone. Of that the $100 million-plus deals taken together (listed in Exhibit 1) represent over 42% of the venture capital invested in biology-driven firms.

To put this in context, large rounds appear to have been responsible for a substantial fraction of the growth in life science venture capital in the last five years. (*See Exhibit 3.*) Between 2013 and 2017, the total amount of venture capital investment recorded in Strategic Transactions grew by nearly $6 billion, more than doubling the 2013 total (116% increase). Rounds under $100 million have grown over that period but only by 42%. Rounds over $100 million account for $4 billion of venture capital growth. If 2018 continues as the first quarter has started, the total of venture investment might rise beyond $16 billion with over $7 billion coming in large $100 million-plus rounds.

So while the amount of venture capital going into life science companies has been increasing since 2013, a transformative change has happened at the upper end of the scale.

Furthermore, while a few of these big chunks of cash arrive as cross-over funding – late-stage rounds that signal an intent to take the investee company public within a timeframe measured in months –the majority is relatively early stage finance, A or B rounds. Between 2013 and the first quarter of 2018, only 25% of the $12.7 billion were in round C or later; the remaining 75% was shared between A and B rounds.

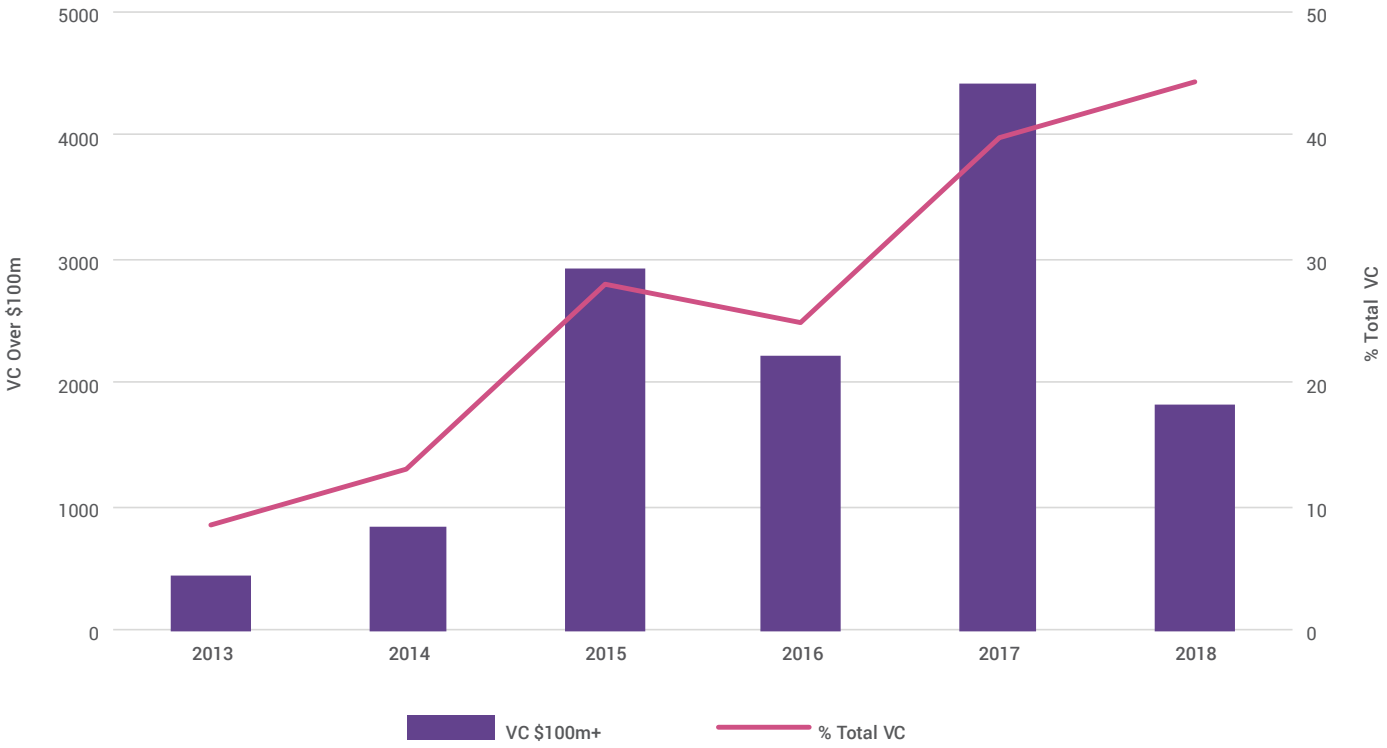
So what is happening here? Are new groups of investors behind this shift in venture investing? Why have these mega-deals emerged? Is it a strategy that applies across the board in life science or are selected area favored? And,

**Exhibit 1: $100 Million-Plus Rounds In 2018**

| Company | $ Million | Round | Focus | Investors |
|---|---|---|---|---|
| Moderna | 500 | Late | mRNA Therapeutics | Abu Dhabi Investment Authority, BB Biotech AG, Julius Baer, EDBI, Sequoia Capital China, Fidelity Management & Research, Pictet, Viking Global Investors, ArrowMark Partners, Alexandria Venture Investments |
| Allogene | 300 | A | Cancer – CAR T cell assets | Pfizer Inc., TPG, University of California, Vida Ventures, BellCo Capital |
| BioNTech | 270 | A | Cancer - mRNA and CART/TCR therapies | Fidelity Management & Research Co., Invus Group, Redmile Group, Struengmann Family Office, Janus Henderson Investors |
| Celularity | 250 | A | Cancer and immune disease - cell therapies | Celgene Corp., Heritage Group LLC, Human Longevity Inc., Section 32, Sorrento Therapeutics Inc., United Therapeutics Corp., Genting Group, Dreyfus Family Office, Section 32 |
| Viela Bio | 250 | A | Autoimmune and inflammatory | 6 Dimensions Capital, Boyu Capital, Hillhouse Capital, Temasek Holdings, Sirona Capital |
| Helix Opco | 200 | B | Genomics | DFJ Ventures, Illumina Inc., Kleiner Perkins Caufield & Byers, Mayo Clinic, Sutter Hill Ventures, Warburg Pincus LLC |
| TCR2 | 125 | B | Cancer - T cell receptor reprogramming | 6 Dimensions Capital, Alexandria Venture Investments, Curative Ventures, F2 Ventures Ltd., Haitong International Securities Group, Hillhouse Capital, Leerink Partners LLC, Lucion Venture Capital Group Ltd., Mirae Asset Financial Group, MPM Capital, Redmile Group, Syno Capital, Cathay Fortune Capital Investment, ArrowMark Partners, Sirona Capital |
| Hua Medicine | 117.4 | D/E | Type II diabetes | 6 Dimensions Capital, Ally Bridge Group, Arch Venture Partners, Eight Roads Ventures, F-Prime Capital , Mirae Asset Financial Group, Ping An Ventures, Venrock Associates, WuXi AppTec Inc. |
| Rubius | 101.2 | C | Red cell allogeneic therapeutics | Cross-over round mutual funds and institutional investors |
| Generation Bio | 100 | B | Gene therapy | Casdin Capital LLC, Deerfield Management, Fidelity Management & Research Co., Foresite Capital Management, Invus Group, Leerink Partners LLC |
| Tmunity | 100 | A | T cell therapies | Gilead Sciences Inc., Lilly Asia Ventures , Ping An Ventures, University of Pennsylvania, Be The Match BioTherapies |

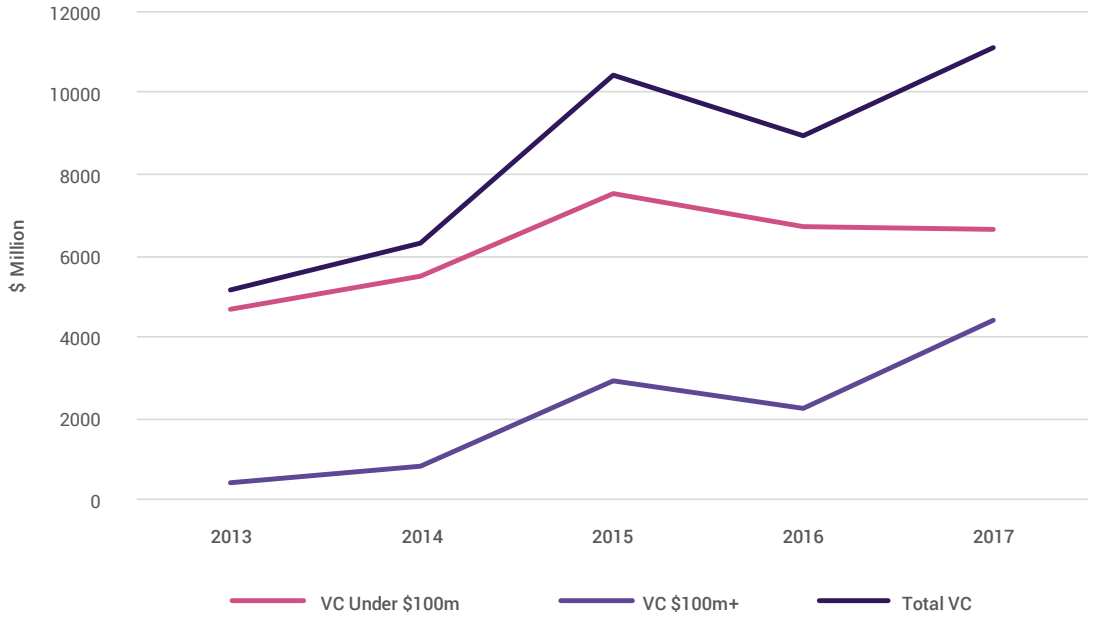
*SOURCE: Strategic Transactions*

## Exhibit 2: The Rise Of The Life Science Mega-Round




*SOURCE: Strategic Transactions*

## Exhibit 3Mega-Rounds Are Fastest Growing Class Of Life Science VC




*SOURCE: Strategic Transactions*

are there strategies that companies need to follow in order to attract the big bucks?

## Which Investors Are Involved

The investor groups behind the big deals are not the run-of-the-mill defensive venture capital consortia. Looking across the board at the large, early rounds, three factors stand out.

The first is that the corporate investment arms of pharmaceutical companies (or medtech, in a few instances) are frequently involved.

Pharma-related funds have become increasingly engaged in venture-stage investing over the past several years. Across the entire spectrum of venture deals, pharma fund involvements increased from under 16% in 2013 to 24% in 2017 (and 27% in 2018 so far). But the pharma's level of involvement the $100-million-plus deals has run at around 40% of each year since 2014 when the phenomenon took off. Pharma money or, more likely, pharma nous is an important component of the venture mega-deal.

Naturally enough pharmaceutical companies are frequently heavily involved in the mega venture rounds that go to companies spun off around their own asset. Thus **Pfizer Inc.** has a 25% ownership stake in **Allogene Therapeutics Inc.** through its recent $300 million A round, **Celgene Corp.** has a stake in **Celularity Inc.** ($250 million A round, February 2018) and **AstraZeneca PLC** has the largest minority stake in **Viela Bio**, which has rights to some **MedImmune LLC** clinical-stage assets and which also raised a $250 million A round in February.

There is no evidence that pharmaceutical company strategic or corporate funds are, themselves, contributing vastly more money. The presence of pharma money in a deal rarely represents a commitment to a particular technological approach or portfolio of early compound. Indeed quite the reverse: commitment is signaled by more direct forms of investment - optioning, asset licensing and acquistion or wholesale M&A.

However, pharma's presence in a large venture capital investment provides the reassurance to deep-pocketed investors that at least the drug industry is watching and interested. Pharma's nous rather than bank account is what is important in the mega-deal.

Another significant element in the mega-deal mix is the participation of large funds with origins in Asia. Generalist groups such as Singapore-headquartered government wealth fund Temasek, Hong Kong's giant investment house Tencent Holdings and the Chinese bank Ping An have become bit hitters in life science venture investments in recent years. The Abu Dhabi Investment Authority and Singapore-based EDBI came in as new investors in Moderna's recent $500 million round. Along with health care specialist investors such as 6 Dimensions Capital (the result of 2017 merger of two Chinese firms, Frontline Bioventures and WuXi Healthcare) and C-Bridge Capital, Asian backers were involved in 28% of the life science mega-deals in 2017 (and in 40% of those in 2018 so far).

The third constituent of many consortia are the blue riband investment companies, particularly US firms such as Fidelity (Fidelity Management and F Prime), Aisling Capital, Redmile, Casdin Capital, OrbiMed, Hillhouse Capital, Arch Venture Partners, Viking Global, Sutter Hill, Leerink Partners, Flagship Pioneering, Venrock and Sequoia Capital.

Add in Woodford Investment Management from the UK (which invested in five $100 million-plus rounds in 2015 and 2016), and these 14 investors have been involved in nearly 70% of the mega venture deals since 2013.

Thus, at the top end of the tree, a rather select group of investors often working in tandem with pharmaceutical company strategic funds and/or large Asian investors, dominates the high-level venture capital funding process.

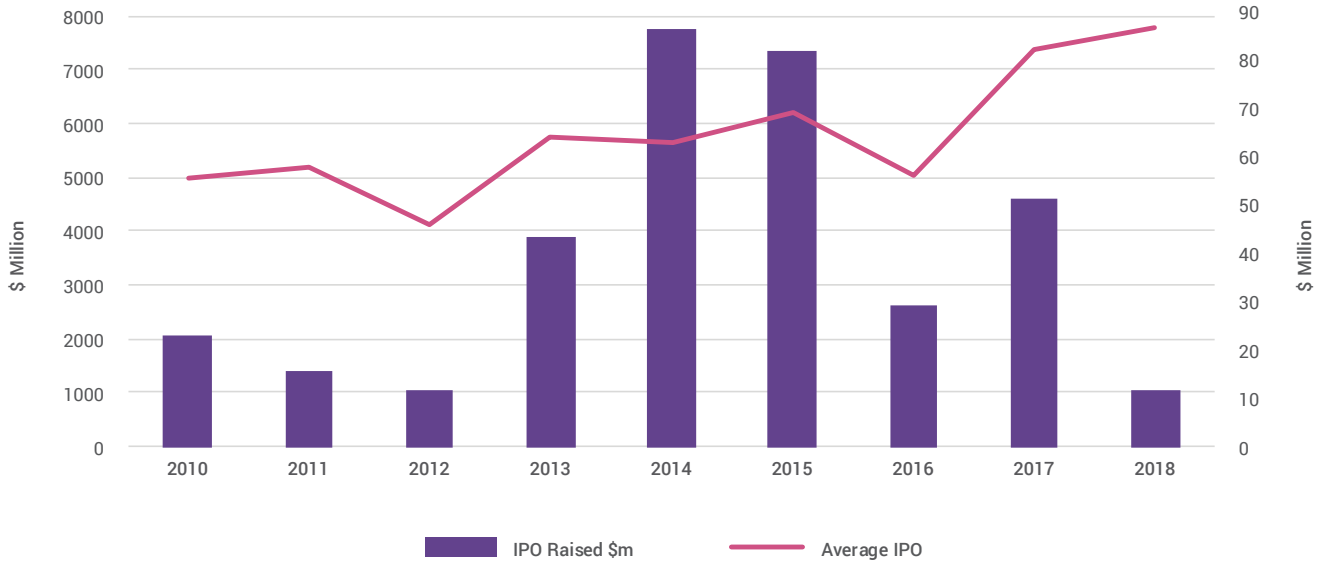
## Why Have Mega-Deals Emerged?

There are a number of reasons for the emergence of much larger numbers of large venture capital rounds. The first is that after a public finance spike, cash-rich venture investors saw an opportunity to take greater control of the fates of their investments.

Venture investors did well in the last open public finance window. With over $15 billion worth of life science initial public offerings in 2014 and 2015, it was relative easy for venture capitalists to demonstrate returns to their limited partners and raise fresh money.

However, as Exhibit 4 shows, the public markets - whose role is to provide venture capitalists with at least partial ex-

## Exhibit 4




*SOURCE: Strategic Transactions*

its and the companies they supported with access to larger quantities of cash - are fickle. In each of 2014 and 2015, IPOs raised over $7 billion. But in the years before that, the IPO baseline was less than a quarter of that level. After the boom, things were a little better: IPOs raised $2.6 billion in 2016 and $4.6 billion (although that figure is inflated by the exceptional flotation of **Actelion Pharmaceuticals Ltd.** spin-off **Idorsia Pharmaceuticals Ltd.** in Switzerland which alone was worth $1.3 billion).

Relying on public markets to provide an escalator for company financing or an exit for venture investors carries its own risk, the chief of which is loss of control of timing. The next public window might coincide with the development path and cash need of newly-formed companies, but then again it might not.

If the fortunes of venture capitalists are not simply to rise and fall at the whim of the public markets, the early investors needed to take control. So rather than hoping against experience for generous and optimistic public markets to be the norm, some players in the life science venture capital have reinvented their own business in a more self-sustaining form.

The VC megadeals, in effect, 'top up' deficiencies in the public markets. (*See Exhibit 5.*)

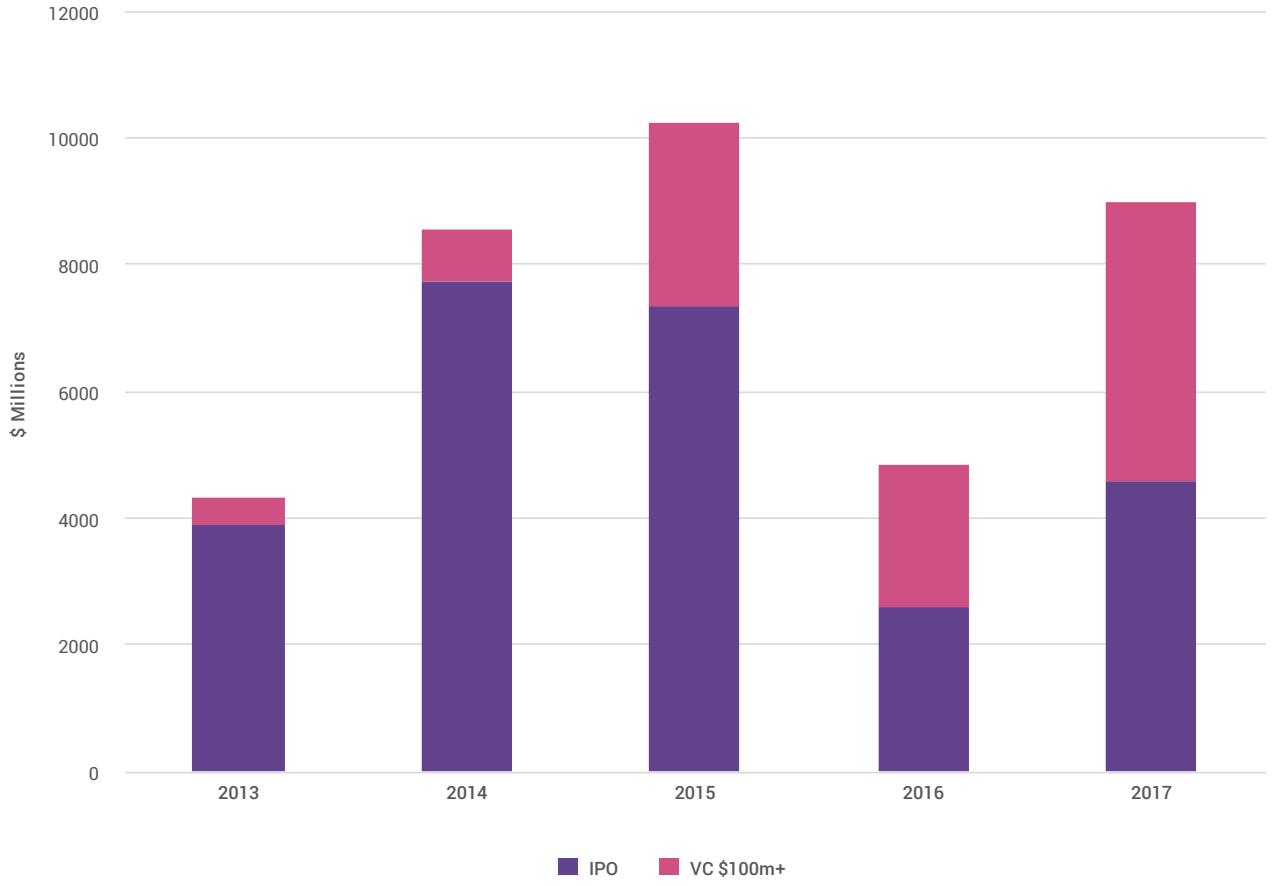
A second driver of the expansion of venture mega-deals was the validation of the value creation models for some technological approaches.

For instance, five of the 10 largest venture rounds of 2018 so far have gone to **BioNTech AG**, Allogene, Celularity, **TCR2 Therapeutics Inc.** and **Tmunity Therapeutics Inc.**, all T cell therapy-related companies. While T cell approaches have not been fully validated either clinically or through revenue generation, their capacity to produce substantial asset value has been validated by, for instance, **Gilead Sciences Inc.**'s $11.9 billion acquisition of **Kite Pharma Inc.** in August 2017 and Celgene's successful bid for Juno Therapeutics, completed in March 2018.

Whether the products being developed by Kite/Gilead and Juno/Celgene ultimately prove themselves clinically superior revenue hogs, it is clear that the assets have a substantial value.

Indeed, Juno's ability to create value was already clear in mid-2015 when, as part a 10-year alliance established between the two companies, Celgene boosted its stake in Juno to 10% stake in Juno. After raising over $300 million between its A round in December 2013 and its B round in August 2014, it took just three-and-a-half years for Juno to close its funding cycle fully.

## Exhibit 5: Megadeal VC Offsets Public Market Fluctuations




*SOURCE: Strategic Transactions*

Furthermore, the commercial activities among the early T cell therapy companies have helped refine the business models and clinical indicators of what is valuable in the field.

In order to extend its reach of its CAR-T cell approach from blood tumors to solid tumors, for instance, Juno partnered with **Editas Medicine Inc.** in May 2015, while it's acquisition of Stage Cell Therapeutics gave it access to a broader range of manufacturing approaches.

Juno as it existed in 2013 would no longer attract the $100 million-plus A rounds. Todays' bar is higher because Juno has run the gamut of what were unknown risks back in 2013.

A third factor in the equation is the globalization of health care technology and, in particular, the opportunities for less developed healthcare systems to overtake more advanced regions in the adoption of new approaches.

Just as the corporate funds of pharmaceutical companies have an unwritten remit that serves to align at least some of their investments with their parent company's main business, so sovereign wealth funds or funds in which government money is prominent will tend to look at business opportunities that play into national economic and strategic plans.

It is quite clear that the US healthcare system itself struggles to accommodate many of the new products that emerge from the pharmaceutical development pipeline. In Europe and Japan, the adoption of new drugs is even more stifled, and outside those developed markets uptake is lower still. Any health care system that remotely resembles the one currently costing the US 19% of its Gross Domestic Product isn't going to work very well in China or in most other Asian nations.

On the other hand, stubbornly persistent of nationalistic notions like the 'not-invented-here syndrome' and pride in domestic manufacture encourage investment in the early stage of new technological developments. The lure of ownership or shared ownership of future advances is a powerful incentive. Consequently, the $800 million that Singapore's Temasek invested for a minority stake in **Verily Life Sciences LLC** (the Google vehicle for health care collaboration) might be seen as a strategic investment on behalf of the future of regional health care.

Kuwait's sovereign wealth fund, the Kuwait Investment Authority was part of a consortium (including communication giant Verizon, Celgene, and private equity company Blackstone) that bet $320 million on healthcare networking firm NantHealth in 2014. And sovereign wealth money from both Saudia Arabia and the United Arab Emirates sits with investments from Apple, Qualcomm and Sharp in the huge $100 billion SoftBank VisionFund. SofBank Vision has been making large, game-changing investments across the tech, health and consumer spheres, including $1.1 billion into drug developer **Roivant Sciences GMBH** and $360 million in liquid biopsy diagnostics company **Guardant Health Inc.**

## Riding The Mega-deal Bandwagon

Unicorns are rare beasts, but in the context of life science investment, small colonies do exist. Although $100 million-plus deals are the fastest growing part of the venture capital scene, there are still only 20 or so deals a year at this magnitude, out 2-300 per year. In 2017, 60% of the venture capital round were worth only $20 million or less.

To attract major amounts of early finance, it will be necessary to attract the attention of pharma or of a consortium of experienced venture capitalists. And you must be in the right technological niche at the right time - not so early that the risks are unknown and not too late that multiple competitors are already close to market. Defining 'the right time' may also depend on the state of the financial markets. But it is difficult to plan for the time when, for instance, the window for public finance is wide open and to coincide a launch just after the point at which venture capitalists' limited partners are recycling their gains.

Nevertheless, the existence of a growing mega-deal market does allow new companies to consider new tactics.

At the outset, for instance, it is increasingly dangerous to use limited intellectual property as the nucleus of a start-up unless as, founders frequently claim, the IP is both unique and essential (it never is). The modern approach, often insisted upon by VCs, is to gather a variety of related approaches under one roof as part of seed-funded activities. That builds in flexibility to a company's business both in it's own R&D and in opportunities for early collaboration.

Companies that have been highly financed may also represent additional exit opportunities for investors in less wealthy firms. It is may be more difficult for pharmaceutical companies to appreciate the value in preclinical projects because their businesses are assessed primarily on the basis of the ownership of market-ready assets that will produce future revenues and profits. In addition, their internal projects may obstruct prospects coming from outside, at least until significant levels of clinical data shouts more loudly. The raison d'etre of well-funded venture-backed firms, on the other hand, is to build pre-market assets as quickly as possible. Anything that speeds that process up, especially through acquisition, is valuable. And that means it is easier to get their attention.

For firms which don't have access to extraordinary levels of venture finance, a viable tactic is to assess not only the progress of their own assets but also to monitor how their better-funded rivals are doing, especially of course if they suffer setbacks. That means not only following their public pronouncements but also cultivating direct communications through meetings and personal contacts. Good information, sanguine comparisons and identification of opportunities at frequent intervals are the keys. Openness is also important: Entrepreneurs are expected to be ambitious but it is unconstructive to mistake ambition for pigheadedness.

Identifying where well-funded firms are struggling may also represent as opportunity for attracting more finance from investors. If unicorns come a-knocking on the acquisition trail, companies that are running on financial fumes may find themselves impaled cheaply on that gleaming horn. Smart management teams know the value of what they have and should ensure that their investors can put them in a position to negotiate.

Heidelberg PHARMA
Focused Cancer Therapies

# ATACs And A New Mode Of Action To Treat Cancer

**German-based and listed Heidelberg Pharma (Xetra:WL6) is building its future on developing Antibody Targeted Amanitin Conjugates (ATACs), which induce tumor cell apoptosis by inhibition of RNA Polymerase II, a new mode of action in cancer therapy.**

Heidelberg Pharma is the first biopharmaceutical company to develop Antibody Drug Conjugates (ADCs) with the toxin Amanitin as a payload, known as Antibody Targeted Amanitin Conjugates (ATACs) to treat cancers. This approach can improve the efficacy of treatments by overcoming resistance to mechanisms, killing dormant tumor cells and creating new options for cancer therapies. Besides building a proprietary pipeline, Heidelberg is open to out-licensing the ATAC technology on a target basis, ATAC third-party collaborations and in-licensing antibodies suitable for proprietary ATAC candidates.

Amanitin, a cyclic octa-peptide derived from the death cap mushroom toxin alpha Amanitin, inhibits RNA polymerase II, an enzyme that is mandatory for cells to transcribe their genes from the DNA to mRNA and subsequently to produce proteins. A lack of RNA Pol II stops important house-keeping mechanisms in the cells and causes apoptosis. This is a novel mechanism of action.

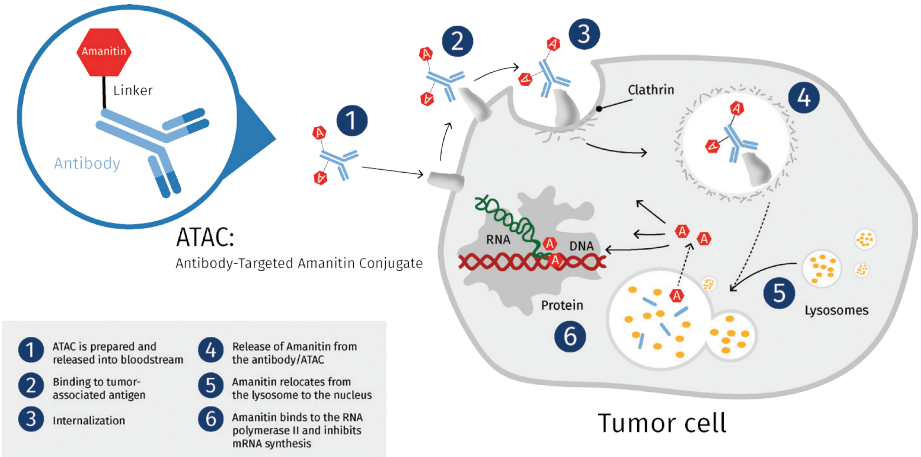
To date the company has shown strong efficacy in preclinical studies with all ATACs. Amanitin has been shown to kill both proliferating and dormant tumor cells, which is expected to increase the ability of these ATAC compounds to prevent metastases and relapse, therefore overcoming resistance and achieving long-term remission.

"We are developing ATACs to treat tumors that no longer respond to standard of care tumor therapy. We believe a targeted treatment of tumors using cytotoxic like Amanitin via highly specific ADCs can produce more effective cancer treatments with acceptable side effect profiles" said Prof Dr Andreas Pahl, CSO of Heidelberg Pharma.

Data of lead candidate HDP-101, a BCMA ATAC to treat multiple myeloma (MM), in animal models and patient cancer cells, have shown HDP-101 has a strong cytotoxic effect at very low doses, even on cancer cells with a low concentration of BCMA antigens and on non-dividing or quiescent cancer cells isolated from MM patients. These data were presented at ASH 2017. Heidelberg Pharma aims to file an IND for HDP-101 and start clinical development 2018.

The company's strategy is to build value through a combination of building an own pipeline and out-licensing the ATAC technology for the development of ADCs by partners. In-licensing antibodies for internal development and later out-licensing, a process that utilizes the 'ATAC tool box' to customize and target-optimized toxins and linkers for partners.

In the last 12 months, Heidelberg Pharma has signed two exclusive multi-target research deals with Takeda and Magenta Therapeutics, respectively. Both deals are worth over $330 million each and both validate the proprietary ATAC technology. In 2017, the company raised €39 million to provide financing for the lead program HDP-101 through proof of concept studies.



# Deals In Depth: March 2018

By Amanda Micklus

Merck & Co and Eisai expanded upon a 2015 trial collaboration and signed a $5.8 billion alliance. Vertical integration in the health care services industry continued with Cigna's $67 billion acquisition of PBM Express Scripts. Siemens Healthineers' $5.2 billion IPO propelled device financing to $6 billion.

### Exhibit 1: Top Alliances In March 2018

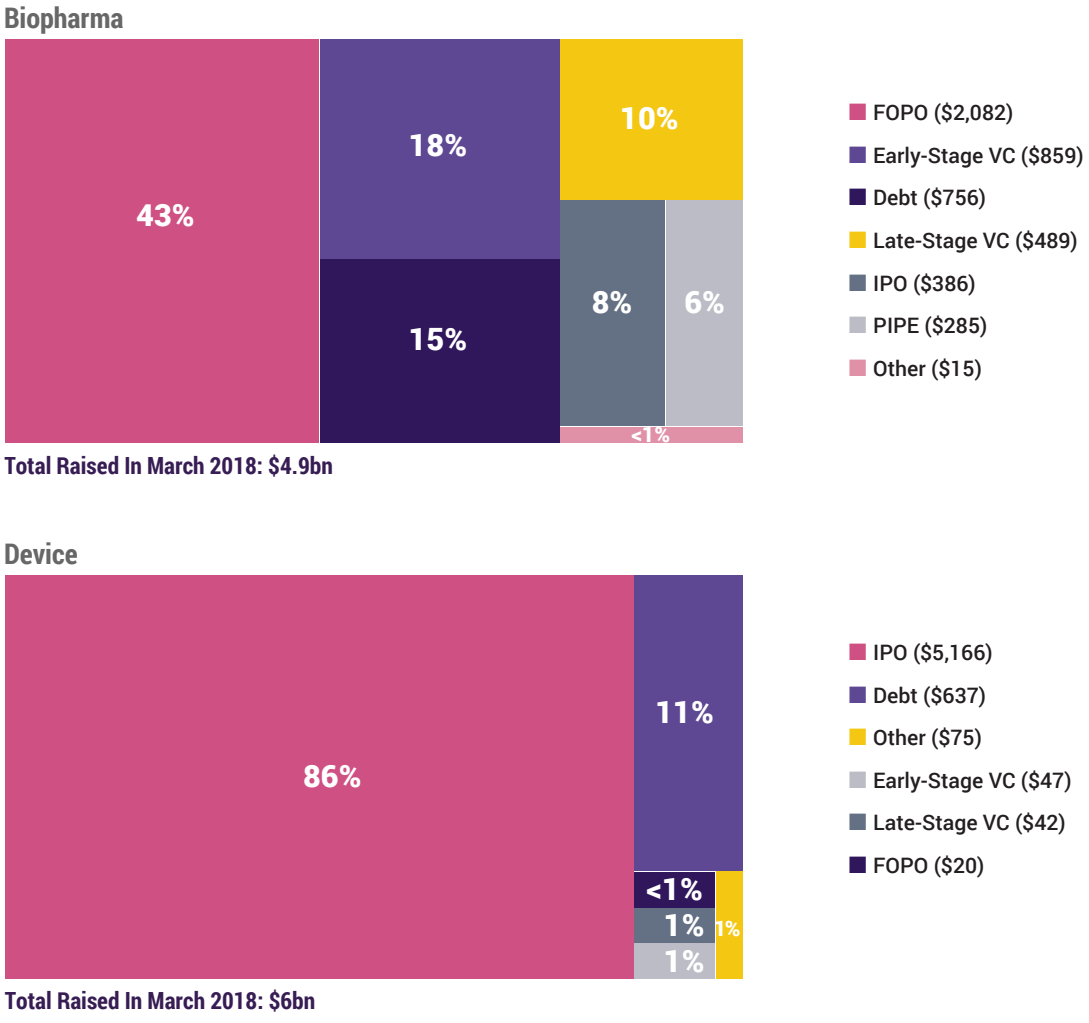

Potential deal value is the sum of up-front fees plus pre- and post-commercialization money

### Exhibit 2: Top Mergers & Acquisitions In March 2018

| Deal Headline | Upfront Total ($m) | Total Earnouts ($m) | Potential Deal Value ($m) | Price-to-Sales (ratio) |
|---|---|---|---|---|
| **Biopharma** | | | | |
| Major vertical integration continues with Cigna's $67bn buy of PBM Express Scripts | 66561 | NA | 66561 | 0.69 |
| Novartis exercises put option for GSK to buy rest of consumer health JV for $13bn | 13000 | NA | 13000 | NA |
| Lundbeck acquires PD-focused Prexton for up to €905m | 123 | 994 | 1117 | NA |
| **Device** | | | | |
| J&J plans to divest LifeScan unit to Platinum Equity for $2.1bn | 2100 | NA | 2100 | 1.4 |
| BD sells Apax its stake in Vyaire JV | 435 | NA | 435 | NA |
| Boston Scientific acquires urology device company NxThera for $306mm, plus earn-outs | 306 | 100 | 406 | NA |

| Deal Headline | Upfront Total ($m) | Total Earnouts ($m) | Potential Deal Value ($m) | Price-to-Sales (ratio) |
|---|---|---|---|---|
| **Diagnostics** | | | | |
| Agilent Technologies agrees to acquire Advanced Analytical Technologies | 250 | NA | 250 | NA |

**Exhibit 3: Financings By Type ($m)**




*Source for all data: Strategic Transactions | Pharma Intelligence, 2018*

# European Life Sciences Start-Ups Maintain Early Investor Allure

By John Hodgson & Mike Ward

- Data compiled by Informa Pharma Intelligence confirms that European life sciences companies witnessed a year-on-year increase in venture cash put to work in 2017. Indeed, European life sciences pocketed more than twice what they raised just five years ago even though the number of companies raising that money has barely moved over the same time period.
- Investors continue to raise additional venture money that is being earmarked for European investments as they seek to tap assets that are less expensive than those being developed by US companies. While much of the venture money raised by European life sciences companies comes from more local sources, the amount coming from non-European sources continues to rise.
- So what? Quality European companies with compelling assets, technologies and data will find it easier to attract increasing amounts of venture financing as investors back larger rounds. Beyond venture financing, however, accessing non-specialist capital from the public markets is likely to remain a major challenge forcing businesses to focus their attention on the deeper pools of capital available to companies listing on US exchanges.

It has never been a better time for life sciences start-ups to raise money from venture sources. In 2017, according to data compiled by Informa Pharma Intelligence, venture capitalists invested a total of $19.7 billion in the sector across the globe – some $15.1 billion allocated to 512 biopharma-focused opportunities while $4.6 billion was invested in 107 medtech businesses. Europe's share of the global take was nearly $4 billion, more than double what it was in 2013.

With new funds being raised and non-European investors looking for bargains, the prospects for European biopharma, medtech and digital health companies going forward looks fairly robust. (*See Exhibit 1*.) However, there are some clouds on the horizon. While the opportunities to raise seed and Series A money in Europe remain buoyant, returning to the capital markets – whether private or public – for the larger boluses of cash required to accelerate growth into sustainable businesses will continue to be a challenge. Moreover, European medical device companies might find raising venture capital more difficult as the regulatory environment becomes more complex.

European biotech entrepreneurs need to be aware that the venture capital industry has other opportunities to get healthy returns. Indeed, European VCs have put similar amounts of money into finance ventures or Internet companies or into consumer enterprise or business services. Looking across all venture investments, health-related VC is around 20% of the $22 billion total in Europe, estimated by FinSMEs, a pan-sectoral investment website. Biotech accounts for around 14% of the total and medtech for about another 3%.

Life sciences companies come out well as recipients of big ticket venture backing, attracting seven of the declared 19 A, B or C rounds in Europe above $50 million in 2017. (*See Exhibit 2*.) However, as if to prove that author Douglas Adams was right all along, the leading B round in Europe in 2017 went to **Improbable**, a British software company developing huge-scale virtual world simulations. It attracted $502 million, just short of the $511 million that the seven big ticket life sciences companies got between them.

Investment in Improbable was led by Softbank Vision, the Japanese-Saudi unicorn backer that also was involved in the CHF1.1 billion investments into pharma developer **Roivant Sciences GMBH** in Switzerland and the $360 million late venture round into US liquid biopsy specialist, **Guardant Health Inc.**

## European Venture Capital Patterns And Exits

Venture capitalists are opportunists, albeit informed ones. Where their money goes depends not only on the qualities

**Exhibit 1: New Money: Funds Raised Since Start Of 2017 That Can Be Deployed In Europe**

| Investor | Fund Name | Most Recent Close | Value $M | Geographies | Focus | Selected Investments Made To Date |
|---|---|---|---|---|---|---|
| Edmond de Rothschild Investment Partners | BioDiscovery 5 | Jan-18 | 428 | 70% EU, 30% RoW | 2/3 Therapeutics, 1/3 Medtech; mainly private | Erytech Pharma SA, LogicBio Therapeutics Inc |
| Athyrium Capital Management & Neuberger Berman | Athyrium Opportunities Fund III | Dec-17 | 1,200 | 80% US, 20% RoW | 50% revenue generating biopharma; 50:50 public:private | OB Hospitalist Group, DuPage Medical Group |
| BioGeneration Ventures | BGV III | Oct-17 | 95 | Seed funding of Benelux & German life science firms | Early stage therapeutic, medtech & diagnostics | NorthSea Therapeutics BV, Mellon Medical BV, VarmX BV, Escalier Biosciences BV |
| BioMedPartners | BioMedInvest III | Aug-17 | 105 | Switzerland, Germany, Austria, France, Italy & Benelux | Early- to mid-stage therapeutics, medical devices & diagnostics | Allecra Therapeutics GmbH, AMAL Therapeutics SA, Cardior Pharmaceuticals GmbH |
| Bay City Capital & GF Xinde Investment Management Co. Ltd | Bay City Capital GF Xinde International Life Sciences Fund | Jul-17 | 200 | Global with focus on US, Canada, Western Europe & China | All stages of development, innovative biopharma | Twist Bioscience Inc, KBP Biosciences, Occulis |
| Atlas Venture | Atlas Venture XI | Jun-17 | 350 | Global | Early stage | Three undisclosed investments are in incubation |
| Medicixi | Medicxi Growth 1 Fund | Jun-17 | 300 | 80% European, 20% US | Growth companies beyond proof of concept with robust clinical data | ObsEva SA |
| Vesalius Biocapital Partners | Vesalius Biocapital III | May-17 | 73 | European | 80% later-stage therapeutics (50%), medtech, diagnostics & eHealth/mhealth | null |
| Ping An Insurance Company of China Ltd | Ping An Global Voyager Fund | Apr-17 | 1,000 | Global specifically in the US, the UK & Israel excluding China | Early-stage digital health | TytoCare Ltd, StartUp Health |
| Mitsubishi UFJ Financial Group Inc | Mitsubishi UFJ Life Science I LP | Mar-17 | 89 | | Seed to late stage therapeutics, regenerative medicine, medical devices & diagnostics | None announced as yet |

| Investor | Fund Name | Most Recent Close | Value $M | Geographies | Focus | Selected Investments Made To Date |
|---|---|---|---|---|---|---|
| Seroba Life Sciences | Seroba Life Sciences Fund III | Feb-17 | 108 | Mainly Irish (50%), UK & Europe with US an option | New companies developing drugs or medical devices | Endotronix Ireland, Prexton Therapeutics SA |
| Advent France Biotechnology | Advent France Biotechnology Seed-Fund I | Apr-17 | 75 | Early French | | None announced |
| Arix Bioscience plc | Raises money from public market | Feb-17 | 117 | Late-stage US and European | | Autolus, Verona Pharma, Artios Pharma |
| High-Tech Gründerfonds | High-Tech Gründerfonds III | Jun-17 | 280 | Mainly early German | Wide range of tech and biology | Zimmer Biotech, Cysal, Venneos GmbH, Sirion Biotech |

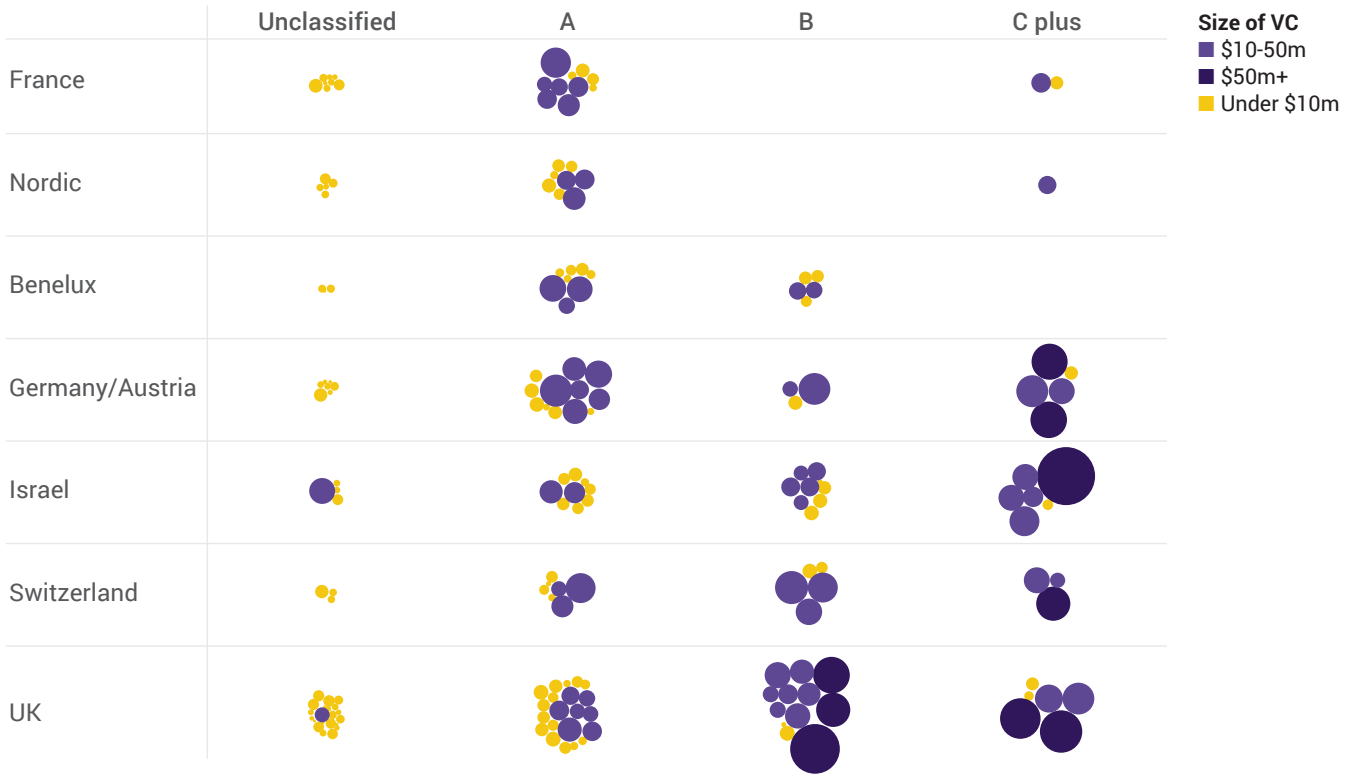
*SOURCE: In Vivo research*

**Exhibit 2: European A-C Rounds Worth More Than $50M In 2017**

| Company | Round size $m | Round | Business | Country |
|---|---|---|---|---|
| Improbable | 502 | B | Simulations | UK |
| Tricentis | 165 | B | Software testing | Austria |
| Orchard Therapeutics | 110 | B | Gene therapy | UK |
| Lilium | 90 | B | Electric jet planes | Germany |
| Cell Medica | 85 | C | Immunotherapy | UK |
| Autolus | 80 | C | T cell therapy | UK |
| ManoMano | 70 | C | DIY marketplace | France |
| Revolut | 66 | B | Banking | UK |
| Iterum Therapeutics | 65 | B | Pharmaceuticals | Ireland |
| Innoviz Technologies | 65 | B | Automotic sensor | Israel |
| Bicycle Therapeutics | 60 | B | Peptide platform | UK |
| MessageBird | 60 | A | SMS platform | Netherlands |
| Hookipa Biotech | 59.6 | C | Biopharmaceuticals | Austria |
| AppsFlyer | 56 | C | Data collection by apps | Israel |
| Xeltis | 51.75 | C | Heart valve restoration | Netherlands/Switzerland |
| Simba | 51.75 | B | Mattress maker | UK |
| Receipt Bank | 50 | B | Bookkeeping | UK |
| Oryx Vision | 50 | B | Autonomous vehicle sensing | Israel |
| Graphcore | 50 | C | Chip design | UK |

*SOURCE: FinSMEs*

**Exhibit 3: Distribution Of Life Sciences (All Segments) VC Investment In European Territories**




*SOURCES: Strategic Transactions; Scrip | Pharma Intelligence, 2018*

of the supplicant companies but also on the routes for getting exits. In the US, public market exits mean Nasdaq but in Europe, options differ.

France, the Netherlands and Belgium have a network of related public stock exchanges designed for small or medium-sized companies – Euronext and Alternext – while the companies in the Nordic region have access to the Nasdaq First North. In theory, all appropriately certified companies have access to these markets, but practical barriers to a single financial market persist.

Nevertheless, the existence of these newish and more adventurous public markets seems to have influenced patterns of venture investment, as *Exhibit 3* illustrates.

In France, the Nordic countries and Benelux, venture funding in life sciences seems almost to be completely focussed on small pre-A and A rounds, with subsequent venture rounds both small and sporadic. This may be because there is an option for companies to list early on Euronext, Alternext or Nasdaq First North.

In contrast, elsewhere in Europe, venture capital in 2017 not only persisted beyond A rounds to B and C and beyond, but the later rounds were often substantial. Rounds in excess of $50 million were not uncommon, particularly in the UK where $50 million-plus rounds appeared in B series financings, too, for two biotech companies, **Orchard Therapeutics** and **Bicycle Therapeutics Ltd.** and for digital health play, **Babylon Health**. (*See Exhibit 4.*)

The pattern might not persist in 2018, but it appears that in some territories, venture capitalists are keen to pass along early-stage risk to public market investors (which may include venture funds with options for public market holdings).

## Funding Local Heroes

Much of the early-stage funding of European life science companies comes from funds that have a more regional, if

**Exhibit 4: Top Venture Capital Rounds In European Life Sciences 2017**

| Company | Size of Round $m | Round | Base | Investors |
|---|---|---|---|---|
| Roivant Sciences GmbH | 1,100 | Undefined | Switzerland | Softbank; Dexcel Pharma; Viking Global Investors; QVT Financial |
| ADC Therapeutics SARL | 200 | D | Switzerland | AstraZeneca; Auven Therapeutics Holdings; Redmile Group |
| InSightec Ltd. | 150 | E | Israel | Elbit Imaging; GE Healthcare Technologies; MediTech Advisors; York Capital Management |
| Orchard Therapeutics | 110 | B | UK | Agent Capital; Cowen & Co.; F-Prime Capital; RTW Investments; Temasek Holdings |
| Autolus Ltd. | 80 | C | UK | Arix Bioscience; Cormorant Asset Management; Nextech Invest Ltd.; Syncona Partners; Woodford Investment Management |
| Cell Medica Ltd. | 73.2 | C | UK | Invesco; Touchstone Innovations; Woodford Investment Management |
| Iterum Therapeutics Ltd. | 65 | C | Ireland | Advent Life Sciences; Arix Bioscience PLC; Bay City Capital; Canaan Partners; Domain Associates; Frazier Healthcare Ventures; New Leaf Venture Partners; Pivotal bioVenture Partners; Sofinnova Partners |
| babylon | 60 | B | UK | NNS holdings; Vostok New Ventures; Kinnevik; Sawaris family |
| Hookipa Biotech AG | 59.5 | C | Austria | BioMedPartners; Boehringer Ingelheim Venture Fund; Forbion Capital Partners; Gilead Sciences; HBM Partners; Hillhouse Capital; Sofinnova Partners; Takeda Ventures |
| Immatics Biotechnologies GMBH | 58 | E | Germany | Amgen; Dievini Hopp BioTech Holding; Wellington Partners Venture Capital |
| InflaRx NV | 52 | D | Germany | Bain Capital Life Sciences; Cormorant Asset Management; RA Capital |
| Xeltis AG | 52 | C | Switzerland | Kurma Life Sciences Partners; Life Sciences Partners; VI Partners; Ysios Capital Partners |
| Bicycle Therapeutics Ltd. | 52 | B | UK | Atlas Venture; Cambridge Innovation Capital; Longwood Fund; Novartis Venture Fund; SR One; SV Health Investors; Vertex Ventures HC |

*SOURCE: Strategic Transactions | Pharma Intelligence, 2018*

not national focus. The most active European fund in 2017 was High-Tech Gründerfonds, a public-private VC investment firm based in Bonn, Germany. It's an early-stage seed investor, focused on high potential high-tech start-ups that are either German or have an independent subsidiary domiciled in the country. In 2017, High-Tech Gründerfonds participated in nine different life science-focused investments.

While not exclusively focused on European opportunities, Forbion Capital Partners, a Dutch VC currently managing

more than €700 million across six closed-end funds, is targeting EU companies primarily on EU targets, as well as Swiss, Norwegian and Canadian opportunities as, according to managing partner Sander Slootweg, comparable US companies have become too expensive. "We invest funds of €200 million on average and our current favorite sectors/areas are metabolic disorders, all viral vector approaches and neurodegenerative diseases," he adds.

Indeed, the most active 13 venture capital groups in European life sciences were involved largely in early-stage investments: 60% of their investments (37 of 62 rounds) were in A rounds or earlier. The 62 investments in European rounds in 2017 were worth $1,175 million, representing just over a quarter of the European Life Sciences VC total.

In many cases, European venture funds have the European Investment Fund as a cornerstone investor and this can place some geographic restrictions on investment activity. Recent funds to get EIF include BGV III the third fund from BioGeneration Ventures, which had a final closing €82 million. BGV III will focus on therapeutics, medical devices and diagnostics within Europe, in particular in Benelux and Germany.

BGV III, which also had backing from **Bristol-Myers Squibb Co.**and **Johnson & Johnson Innovation**, has already made five investments from the fund into German immuno-oncology company **CatalYm GMBH**, and Dutch companies **Escalier Biosciences BV** (autoimmune diseases), **Scenic Biotech BV** (target discovery), **Varmx BV** (hematology) and **Mellon Medical BV** (vascular suturing).

There has been some concern that EIF backing for many European funds could have a negative impact on the ability of UK companies to access such money post-Brexit. While it is true that UK firms will find themselves chasing after smaller sums allocated to non-EU companies by these funds, there is a confidence within boardrooms and among investors that quality companies need not be worried. EIF was one of the cornerstone investors in TVM's TVM LSV, a fund created in 2005. "Conditions at that time were that a majority of the capital be invested in Europe. We do not see any impact post-Brexit on TVM LSV VI. We are currently investing from Fund VII and preparing to raise Fund VIII, both without participation of the EIF," explains Hubert Birner, PhD, a managing partner at the German VC.

"We are looking for innovative companies in North America, Europe and Asia that have the potential for disruption in their sector; and who are looking for a VC who can help them accelerate. Which in our case means provide in-depth global industry insight and a closely knit network as well as the necessary, very specialized, operational experience in this industry. None of these are impacted by Brexit," adds Birner.

Interestingly, proximity to investee companies is a major driver for many venture capitalists that are not constrained by geographic restrictions. SVLS, the UK-based life sciences fund, is not restricted to the UK but tends to invest closer to home. "We have no predetermined allocation but invest mostly in UK deals because the management is stronger and the environment is more conducive," notes SV Life Science's managing partner Kate Bingham.

Nevertheless, Bingham will look further afield. Last fall, the Dementia Discovery Fund, created in 2015 with support from the UK government and five pharma companies to fund novel biology for neurodegenerative disorders and managed by SVLS, led the $29.5 million in a Series D round in

**Alector LLC**, a San Francisco-based company developing preclinical immunomodulatory therapies to treat neurodegenerative disorders including Alzheimer's disease.

While acknowledging the European life sciences sector is an exciting environment with many excellent investment opportunities, Abingworth managing partner Tim Haines remains agnostic to geography.

"We aim to invest in the best opportunities in life sciences, whether these are in the US or Europe. We invest primarily in therapeutics with an emphasis on early-stage deals. However, while there is no specific allocation between territories, our portfolios to date have been split roughly 60/40 between the US and Europe," he says.

Although immuno-oncology is all the rage, and has attracted the most venture dollars, many VCs are looking to other sectors. Forbion invests funds of €200 million on average. SVLS' Bingham adds, "For IO deals, we need to believe we can generate persuasive, differentiated profiles given how busy the field has become." She prefers to focus on immunology and CNS, especially dementia.

## Going Global

While much of the money put to work in European life sciences is linked to regional and local funds, interest from global investors such as OrbiMed confirms that quality opportunities in Europe can attract funds. "While the majority of our investments are in the US we see a lot of exciting European companies that don't have as many investor dollars chasing them. Indeed, there can be more opportunity to work with companies in Europe than say Boston or San Francisco where there are lots of investors closing deals," Carl L. Gordon, PhD, general partner and co-head of Global Private Equity at OrbiMed, tells *In Vivo*.

Even though OrbiMed does not have an office in Europe nor a specific allocation for European businesses, according to our data, it ranked just below the largely-German seed funder, High-Tech s, for investor activity in the region in 2017. OrbiMed participated in 33 life sciences venture investments in 2017, nine of which were in European businesses. But OrbiMed is geographically agnostic, so European businesses must compete against US opportunities from OrbiMed's current $1 billion global VC fund, OrbiMed Private Investments VII.

"Our main focus is on companies developing therapies that are truly novel in their approaches at any stage in the development cycle from preclinical assets through to ready-for-market drugs. To a lesser extent, we will look at diagnostics, digital health and medical devices but at a much later stage," Carter Neild, a general partner at OrbiMed, adds.

OrbiMed has two venture partners with close ties to Europe – Iain Dukes, DPhil, who was previously as senior vice president, business development and licensing at MSD, and Klaus Veitinger, MD, PhD, who was on the executive board of Schwarz Pharma AG and CEO of Schwarz Pharma Inc. These industry veterans will take board positions on European companies that OrbiMed invests in as well as provide them operational decision support.

Not surprisingly, cancer, neurodegenerative and rare diseases top OrbiMed's wish list.

## Israel Flies The Banner For Medtech

Medtech investment in the European Union has largely ground to a halt probably because of the substantial tightening of regulatory constraints, but continues apace in Israel.

*Exhibit 7* illustrates that in 2017, medtech companies from Israel (~8.5 million people) attracted almost as much venture investment - $285 million - at all stages in the financing process as companies across the whole of the rest of Europe ($348 million; ~525 million people).

Medtech investments accounted for over half of all life sciences venture capital going into Israel ($285 million out of $495 million). Half of the Israeli total ($150 million) went to **Insightec Ltd.**, which is developing magnetic resonance imaging-guided focused ultrasound surgery, in what is believed to be the company's last pre-IPO venture round.

To tap into such opportunities, OrbiMed established a dedicated Israeli fund although its focus is evolving. Having initially focused on medtech opportunities, OrbiMed's Gordon notes that the firm is seeing opportunities in emerging biotherapeutics. "We set up the Israeli fund because we identified a lot of opportunities in the Israeli medtech space but biotech is emerging there. However, our investments in the Israeli therapeutics space tend to be much earlier than we would do in either the US or Europe," he adds.

Medtech, however, is losing some of its luster. Forbion Capital, for example, used to put about 30% of its funds into medtech companies but has now downgraded that allocation to about 15%."Medtech in our view has become less attractive because of a more restrictive regulatory environment in Europe and more cumbersome reimbursement procedures. In addition, public markets in general have been less receptive for medtech stories, compared with biopharma and there are fewer buyers in this space left, after massive consolidation has occurred in the past decade, so acquirers can afford to wait a little longer. This forces our companies typically into early commercialization activities, with limited means and typically only one product to sell, this is not very economical," notes Forbion's Slootweg.

## Growth Capital Opportunities

Getting access to the large boluses of cash companies need to build their businesses remains a challenge for European companies but there are a growing number of options. "Funding always remains a concern. Anecdotally we know that compared with US CEOs, European CEOs

## Exhibits 5 And 6: Venture Investors in European Life Sciences*

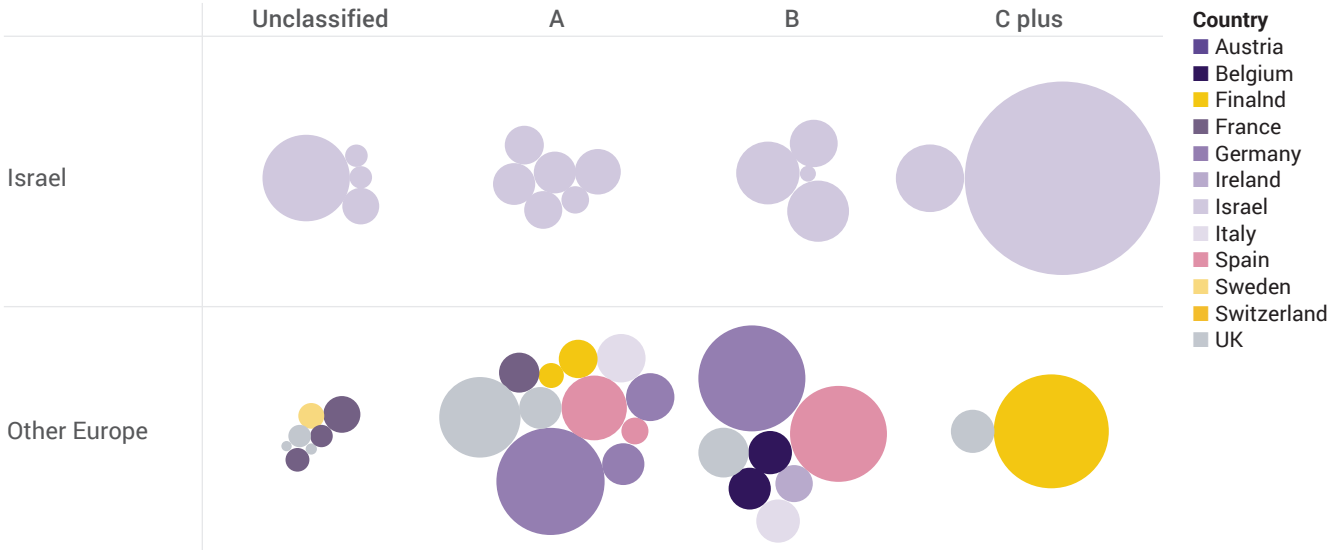
| Investor | European rounds 2017 | European Rounds as % of Global rounds | Based in |
|---|---|---|---|
| **Most Active by Number of Rounds** | | | |
| High-Tech Gruenderfonds | 12 | 100% | Germany |
| OrbiMed | 9 | 27% | US |
| Novo AS | 9 | 50% | Denmark |
| Life Sciences Partners | 8 | 89% | Netherlands |
| Kurma Partners | 8 | 100% | France |
| Sofinnova | 7 | 41% | France/US |
| Boehringer Ingelheim Venture Fund | 7 | 88% | Germany |
| Seventure Partners | 7 | 88% | France |
| Johnson & Johnson Development Corp. | 6 | 40% | US |
| Forbion Capital Partners | 5 | 71% | Netherlands |
| Ysios Capital | 5 | 71% | Spain |
| Pontifax | 5 | 83% | Israel |
| BioMedPartners | 5 | 100% | Switzerland |
| Idinvest Partners | 5 | 100% | France |

| Investor | Total Mean Contribution $m** | # European Rounds | Base |
|---|---|---|---|
| **Most Active in A, B and C Rounds by Size of Round**** | | | |
| Life Sciences Partners | 48.93 | 8 | Netherlands |
| Touchstone Innovations | 43.31 | 4 | UK |
| Woodford Investment Management | 40.4 | 3 | UK |
| Sofinnova | 40.23 | 7 | France/US |
| Ysios Capital | 39.04 | 5 | Spain |
| Novo AS | 36.47 | 9 | Denmark |
| Kurma Partners | 34.29 | 8 | France |
| Boehringer Ingelheim Venture Fund | 33.69 | 7 | Germany |
| OrbiMed | 31.44 | 9 | US |
| Forbion Capital Partners | 30.98 | 5 | Netherlands |
| F-Prime Capital Partners | 29.47 | 3 | US |

| Investor | Total Mean Contribution $m** | # European Rounds | Base |
|---|---|---|---|
| **Most Active in A, B and C Rounds by Size of Round**** | | | |
| Abingworth Management | 29.18 | 2 | UK |
| Invesco Ltd. | 28.13 | 2 | UK |
| TVM Capital | 28 | 2 | Germany |
| Syncona Partners LLP | 27.25 | 2 | UK |
| Arix Bioscience | 27.22 | 4 | UK |
| Novartis Venture Fund | 24.85 | 4 | Switzerland |
| Seventure Partners | 24.67 | 7 | France |
| Versant Ventures | 20.18 | 2 | US |
| GIMV | 19.69 | 2 | Belgium |
| New Enterprise Associates | 19.25 | 2 | US |
| High-Tech Gruenderfonds | 18.1 | 12 | Germany |

*SOURCES: Strategic Transactions; Scrip | Pharma Intelligence, 2018*

**Exhibits 7: Medtech Investment In 2017: Europe Vs. Israel**




*SOURCES: Strategic Transactions; Scrip | Pharma Intelligence, 2018*

spend more time raising their rounds –which means they must be distracted to some extent from other tasks. The funding challenge is specifically at the B round when choice of public, M&A, large B round, etc. is being made," explains Nooman Haque, a managing director at Silicon Valley Bank.

Where to go public is always a challenge for European life sciences companies. Although there has been an uptick in European IPOs in recent years, companies listing on European exchanges face a number of challenges. First, the amount of money that can be raised in Europe is nowhere the same level that is achievable in the US. Second, analyst coverage in Europe is both limited in terms of quantity and quality. Third, and probably most important long term, liquidity and access to substantial follow on financing is a major stumbling block.

While European companies can raise equivalent sums to US firms in the early years, the amount of money available subsequently is much lower in Europe. This creates opportunities for investment firms to create specific growth vehicles.

Medicxi Ventures last year, with support from Verily Life Sciences, a subsidiary of Google parent company Alphabet, Novartis and the European Investment Fund, established Medicxi Growth 1 – a $300 million fund focused on investments in emerging companies with drug candidates in Phase IIb and beyond.

From MG1, Medicxi intends to lead syndicates, putting in €10-€25 million per company, with about 80% earmarked for European companies and the remainder going into US opportunities. To date, MG1 has anchored the $96.8 million IPO of **ObsEva SA**, a Switzerland-based women's health company, and invested in the Cleveland, OH-based diabetes company **Diasome Pharmaceuticals Inc.**.

OrbiMed is already providing substantial growth capital through a dedicated $1 billion fund focused on structured finance and royalty-based financing, OrbiMed Royalty Opportunities II, explains Matthew Rizzo, a partner in OrbiMed's credit business. "We focus on later-stage opportunities, for example in companies that are building out commercial infrastructures, making acquisitions, or in-licensing products. Investments can be substantial, upwards of $150 million, ideally with commercial-stage innovative products and strong intellectual property."

A One European company to benefit from such support is the Dutch biopharma company **Pharming BV**. "We saw an interesting opportunity in a rare disease-focused company with an under-appreciated asset that needed a minimally-dilutive financing solution," he says. In 2017, OrbiMed provided Pharming with a four-year $100 million senior secured debt facility to refinance debt on more favorable terms to redeem a total of €35.9 million of amortizing convertible bonds and refinance $40 million of senior debt.

# Polyglucoferron: a new benchmark for IV iron treatment

**iron4u was founded in Denmark in 2012 by investors from 5 European countries – including Germany and Denmark.**

**iron4u's main focus, in cooperation with the German Company Serumwerk Bernburg, is to develop and register a patented human injectable iron product based on Polyglucoferron and to market the product world-wide.**

**The company focuses on improving the treatment of iron deficiency for humans. In addition iron4u have marketed products aiming at optimizing treatment of iron deficiency in the veterinary setting.**

**Discussions with licensing partners are ongoing.**

Maintaining normal iron levels in the blood and bone marrow is essential for optimal functioning of the human body. Iron is a core component of enzymes and proteins involved in key metabolic processes such as DNA synthesis, cell proliferation and differentiation, cellular respiration or immune protection against bacteria.

Most importantly, iron is an essential element in the production of hemoglobin, the blood protein that transports oxygen from the lungs to the tissues. An estimated 70% of human iron is found in the red blood cells that contain *hemoglobin* or the myoglobin protein expressed in the body's muscle cells.

In terms of mass, iron is the most abundant natural element on earth. Yet iron deficiency remains a significant challenge to human health worldwide, diminishing in a variety of ways the quality of life of the many people whose iron levels are too low.

## Deficiency is widespread

Iron deficiency can occur as a result of malnutrition, malabsorption of iron, or diseases and conditions that deplete iron either directly or indirectly, such as peptic ulcers, inflammatory bowel disease, colorectal cancer, major surgery or excessive menstrual bleeding.

According to the World Health Organization (WHO), iron deficiency is the most common and widespread nutritional disorder of all. Some two billion people in total, or more than 30% of the global population, are anemic – many of them due to iron deficiency.

In developing countries, where an estimated 50% of pregnant woman and 40% of preschool children are anemic, iron deficiency is often exacerbated by worm infections, malaria and other infectious diseases such as tuberculosis, HIV/AIDS or schistosomiasis. The true scale of the problem is hidden behind health statistics such as death rates, incidents of maternal hemorrhage or poor performance in schools.

Ultimately, though, iron deficiency is a global public-health issue, one of epidemic proportions. For example, lack of iron is the only nutrient deficiency with significant prevalence in industralized countries.

## Health and economic impact

The health consequences of iron deficiency include poor outcomes in pregnancy, with anemia contributing to 20% of all maternal deaths worldwide, as well as impaired physical and cognitive development, increased risk of child morbidity, and reduced productivity in adults.

By undermining the capacity of individuals or entire populations to work and prosper, lack of iron has grave implications for economic health and national development. Timely and effective treatment of iron deficiency can both restore personal health and raise national productivity levels by as much as 20%, the WHO notes.

## Unmet need

These high levels of unmet need have persisted despite the general availability of fortified foods, iron supplements and, in severe cases, blood transfusions to treat iron deficiency.

In many countries, though, the options for convenient intravenous (IV)

Photo credit: Iron4u

*Iron4u headquartered at Næsseslottet, a historical manor from the 1780's located only 20 minutes from Copenhagen.*

administration of high-dose iron are limited, not least due to the associated risk of severe adverse events.

Lower-dose IV iron products, on the other hand, raise questions of effectiveness, convenience and cost-efficiency. Patients often need to make multiple visits to a hospital before they can reach optimal levels of iron in the body.

## A new benchmark for IV iron

At Iron4u, a pharmaceutical company founded in 2012 by investors from five European countries and based just outside Copenhagen, Denmark, we have addressed these issues by developing an innovative high-dose IV iron product for the treatment of iron deficiency or iron-deficiency anemia.

We believe Polyglucoferron could set a new benchmark in the field of intravenous iron therapy. Developed in partnership with the German company Serumwerk Bernburg, the product is now in Phase III clinical trials for human use as an injection or infusion.

Once approved and launched, Polyglucoferron is expected to fill a significant gap in the market for IV iron treatments capable of providing the high doses demanded by current deficiency levels worldwide, yet without compromising patient safety.

Polyglucoferron is a patented total-dosage iron therapy with a unique formulation and an ideal pharmacokinetic profile. Unlike some currently available IV iron formulations, our product is based on modified starch rather than dextran.

"We have encapsulated iron nanoparticles in such a way that they form a larger and stronger complex than other IV iron products. This means Polyglucoferron can deliver high doses of intravenous iron while ensuring that they are cleared rapidly from the plasma, thus minimizing the patient's exposure to potentially damaging free iron," says Iron4u's Medical Director, Stig Waldorff.

## Massive potential

"Our market analyses indicate that the commercial potential for a truly effective and well-tolerated IV iron treatment is enormous," says President and CEO Odd Vaage-Nilsen.

"Intravenous iron sales in the US alone are set to reach $1 billion within a few years. In the longer term, the US market could be worth more than $5 billion. The high levels of unmet need for iron-deficiency therapy worldwide suggest a wealth of opportunities for rapid growth with the right product."

We also want to make sure that Polyglucoferron is available across a broad spectrum of unmet needs. That includes the particular challenges of treating iron deficiency in children, which can have serious long-term consequences for growth, development and immunity to infection.

In this respect, we achieved an important milestone on 1 December 2017, when the European Medicines Agency (EMA) agreed to our pediatric investigation plan (PIP) to study Polyglucoferron in patients aged 6 months to 18 years.

We expect shortly to publish the results of our Phase II clinical trials in adults, which confirmed Polyglucoferron's highly attractive product profile. "After many years of working on improved options for iron-deficient patients and their clinicians, Iron4u is well on the way to redefining the standard of care for IV iron therapy," Vaage-Nilsen comments.

# BIOPHARMA QUARTERLY DEALMAKING STATISTICS, Q1 2018

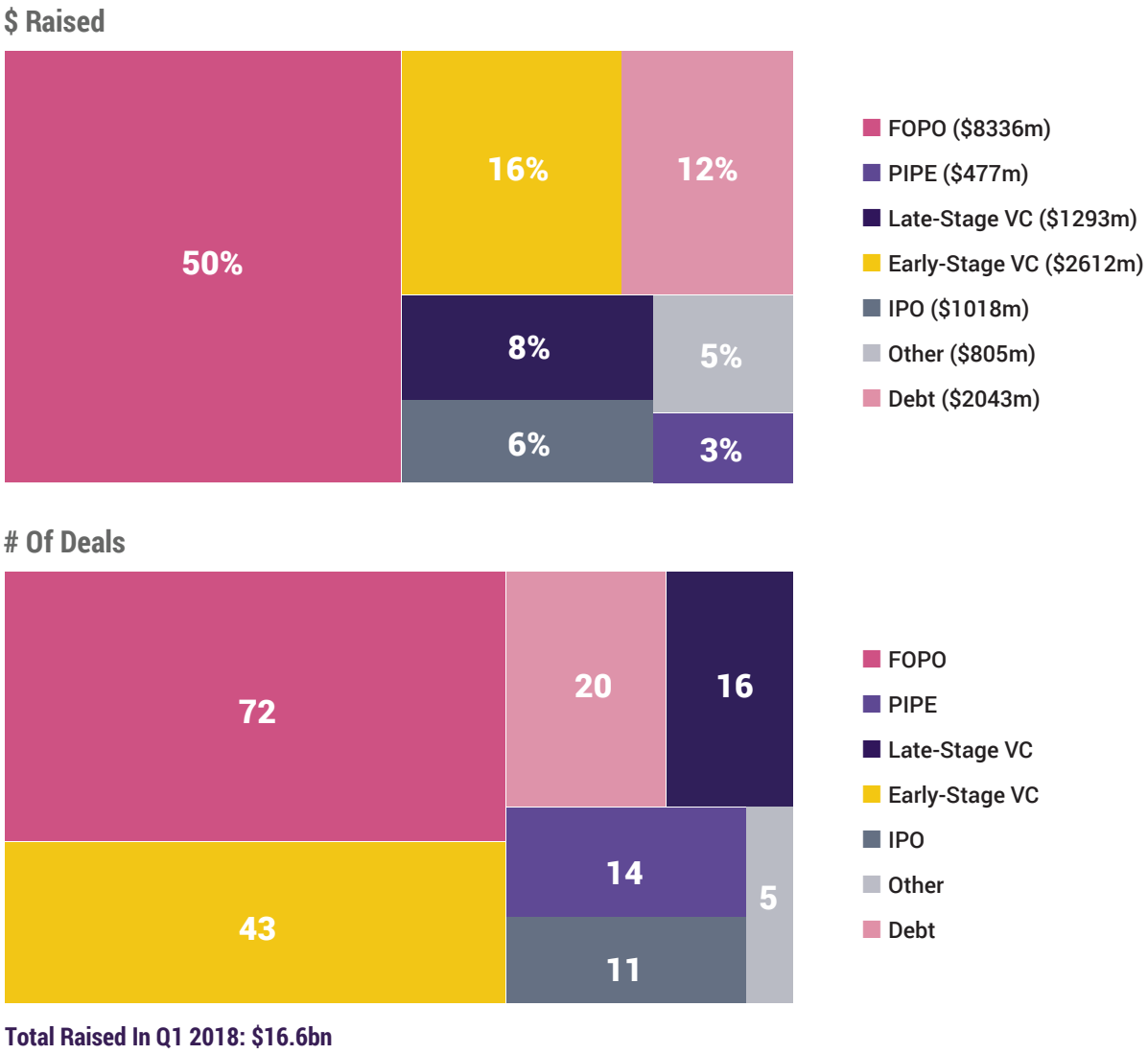
## A look at financing, M&A and alliance activity January–March 2018

By Amanda Micklus & Maureen Riordan

### Financings

Biopharma financing value for the first quarter of 2018 reached $16.6 billion, 14% more than Q4 2017's $14.5 billion. (*See Exhibit 1.*) Mostly the growth was due to a surge in follow-on public offerings, 72 of which together brought in $8.3 billion. This represented half of all Q1 financing activity, an increase in deal volume over last quarter's 52 FOPO transactions, and a 58% rise in dollar volume over Q4's $5.3 billion FOPO total.

**Exhibit 1: Q1 2018 Biopharma Financing By Deal Type**




**Total Raised In Q1 2018: $16.6bn**

*SOURCE: Strategic Transactions | Pharma Intelligence, 2018*

Three out of the four top FOPOs (and also many of the top deals across all financing categories) were in cancer: **BeiGene (Beijing) Co. Ltd.** (immuno-oncology), $758 million; **Seattle Genetics Inc.** (targeted antibody-based cancer therapies), $659 million; and **Agios Pharmaceuticals Inc.** (cancer and rare genetic disease drug development focused on cellular metabolism and precision medicine), $516 million. CNS-focused firms **Sage Therapeutics Inc.** and **AveXis Inc.** both also had FOPOs among the top-10 largest financings for Q1, netting $549 million and $432 million, respectively.

At $2.6 billion, the early-stage venture round category made up 16% of the Q1 total and 26% more than last quarter's $2 billion aggregate with just slightly fewer deals. The biggest standout is cancer immunotherapy company **BioNTech AG**'s January $270 million Series A round. *(Also see "BioNTech COO Sean Marett Reveals How To Spend $270M" - Scrip, 12 Apr, 2018.)* The biotech also concurrently partnered with **Scancell Ltd.** in a collaboration that leverages each other's respective technologies (BioNTech's high-throughput cloning platform and Scancell's *Moditope* cancer vaccine program) to develop T-cell receptor-based therapeutics for cancer.

Declining just slightly from what the category brought in last quarter ($1.5 billion), late-stage VC rounds were down in Q1, totaling $1.3 billion through 16 transactions. The biggest late-stage amount was raised by **Moderna Therapeutics LLC** through its $500 million round, accounting for just under half the full-quarter late-stage total. The mRNA therapeutics company will use the proceeds to advance development of its pipeline of 19 candidates (including 10 in the clinic); for drug discovery in rare diseases and prophylactic vaccines; and for investments in mRNA science, digital tool technologies, and manufacturing infrastructure.

Venture capital rounds of $100 million or more are becoming more common, and during the opening quarter of 2018 alone, there were nine companies bringing in such investments and thus accounting for $1.8 billion or 47% of the Q1 $3.9 billion VC funding total (across both early- and late-stage categories). *(Also see "Billion Dollar Bets, Health Care Magic" - In Vivo, 25 Apr, 2018.)*

Although markedly lower than Q4's $3 billion aggregate, debt was also a big category during Q1 with 20 companies together raising $2 billion, and accounting for 12% of the quarter's total. Respiratory disease-focused **Insmed Inc.** netted the most in its $436 million underwritten public offering of 1.75% convertible senior notes due 2025. Six other companies also had debt raises exceeding $100 million, including three players in the neurology space: **Supernus Pharmaceuticals Inc.** (drug reformulations) netted $391 million through the private placement of senior notes; **Alder BioPharmaceuticals Inc.** (antibody therapeutics) netted $242 million in an underwritten public offering of senior notes; and **Corium International Inc.** (transdermal delivery for biologics and small-molecule drugs) raised $100 million through the private placement convertible senior notes to qualified institutional purchasers.

Eleven companies completed initial public offerings – together bringing in net proceeds of $1 billion (with an average deal value of $92.5 million) – down from last quarter when 15 companies listed for an aggregate $1.7 billion, but still a good start for the year versus the beginning of 2017 when there were only two finalized IPOs. Of the companies IPOing in Q1, seven were start-ups, including three-year-old rare genetic medicines firm **Homology Medicines Inc.**, which finalized a $154 million IPO, Q1's largest. While the predominant therapeutic area was cancer (with five companies involved in this space completing Q1 IPOs), other therapy areas were also well represented.

One of these areas was dermatology. Israeli biotech **Sol-Gel Technologies Ltd.** (topical drug therapies) – the only company headquartered outside the US to complete a Q1 IPO – netted $80 million in its Nasdaq listing. Two other dermatology-focused companies also went public during Q1. **Evolus Inc.** (neurotoxin development and manufacturing for medical aesthetics) netted $56 million and **Menlo Therapeutics Inc.** (developing NK-1 antagonist serlopitant (VPD737) in-licensed from **Merck & Co. Inc.**for chronic pruritus) netted $127 million.

Also of interest is **BioXcel Therapeutics Inc.** (artificial intelligence (AI) platform to identify neuro and immuno-oncology drugs), which netted $56 million in its March IPO. BTI's *EvolverAI* platform integrates millions of fragmented data points using AI, big data analytics, and machine-learning algorithms to enable the identification of lead programs selected due to their strong potential. The company believes its method will enable the design of more efficient clinical trials and speed up time to market; BTI hopes to advance its pipeline using the FDA's expedited 505(b)(2) regulatory pathway.

**Exhibit 2: Digital Therapeutic Firms Play Active Role in Recent Financing Activity**

| Date | Company (Description) | Lead Compound(s)/Phase/ Indication(s) | Financing Type | Amount Raised ($m) |
|---|---|---|---|---|
| Apr. 2018 | BenevolentAI (bioscience machine brain; incorporates algorithms, deep-learning linguistic models, and AI tools for drug discovery and development | BEN2001/Phase IIb/ADHD, Parkinson's; Pipeline of early-phase programs in glioblastoma, sarcopenia, and rare diseases | Series B (assumed) | 115 |
| Jan. 2018 | Centrexion (big data analytics/ translational medicine) | CNTX4975/Phase II/Pain | Series D | 67 |
| Oct. 2017 | Recursion Pharmaceuticals (AI and biology screening/discovery platform) | Pipeline of over 30 discovery to preclinical programs/Multiple rare disease areas | Series B | 60 |
| Mar. 2018 | BioXcel Therapeutics (EvolverAI big data analytics and machine-learning algorithms platform for drug identification) | BXCL501/Phase I/Neurodegenerative and psychiatric disorders | IPO | 56 |
| Jan. 2018 | Pear Therapeutics (drug/software combinations) | reSET/FDA approved/Substance use disorder; reSET-O/Phase III/Opioid use disorder | Series B | 50 |
| Mar. 2018 | TwoXAR Inc. (AI drug discovery) | TXR411/Preclinical/Type II diabetes | Series A | 10 |
| Apr. 2018 | ReviveMed (AI discovery and development using biomarkers and metabolomics data) | Discovery programs in metabolic and non-alcohol fatty liver disease | Seed | 1.5 |

*SOURCE: Biomedtracker, Pharmaprojects, Strategic Transactions | Pharma Intelligence, 2018; Company websites*

Multiple companies with AI platforms have also recently raised money across various financing vehicles. (*See Exhibit 2.*) The biggest to date is **BenevolentAI** (digital healthcare platform it calls a "bioscience machine brain;" incorporates algorithms, deep-learning linguistic models, and AI tools), which brought in $115 million (at a pre-money valuation of $2 billion) during April 2018, in what appears to be its Series B round, from new investors as well as existing backers. Also of note is **Pear Therapeutics Inc.** (drug/software combinations focused on treating behavioral health disorders), which raised $50 million in a January Series B round followed by partnerships in March with Novartis (in the area of multiple sclerosis and schizophrenia) and in April with the Big Pharma's **Sandoz International GMBH** division to commercialize Pear's *reSET* digital therapeutics for substance abuse.

## Acquisitions

First quarter 2018 biopharma merger and acquisition deal value reached a record $116.4 billion, topping (by 18%) the previous all-time-high set with Q4 2017's $98.3 billion M&A total (which was mostly from **CVS Health Corp.**'s $77 billion takeover of **Aetna Inc.**) Like in Q4 2017, a significant portion of this quarter's total (58% this time) is from a single transaction – **Cigna Corp.**'s definitive agreement in March to buy pharmacy benefit manager (PBM) **Express Scripts Holding Co.** for $67 billion – and again falls within the services space. Not counting this outlier, the Q1 M&A total (at $49 billion) is still a hefty sum and includes eight billion-dollar-plus transactions. (*See Exhibit 3.*)

Cigna's takeover of Express Scripts positions Cigna strongly in the PBM market, where it previously had only a small presence. Express Scripts manages prescription drug benefits for a wide variety of customers, including managed care organizations, health insurers, third-party administrators, employers, union-sponsored benefit plans, workers' compensation plans, government health programs, providers, clinics, and hospitals. The company derives revenues

**Exhibit 3: Top Biopharma M&As, Q1 2018**

| Date | Acquirer/Acquired (Business) | Terms |
|---|---|---|
| Mar. | Cigna/Express Scripts (PBM) | $67bn: $96.02 ($48.25 in cash and 0.2434 in the combined company's stock) per share, a 27% premium; 0.67x sales |
| Mar. | GSK/Novartis' stake in 2014 consumer health JV | $13bn in cash for Novartis' 36.5% share in JV |
| Jan. | Sanofi/Bioverativ (hemophilia and other rare blood disorder therapeutics) | $11.4bn: $105 in cash per share (a 73% premium); 13.07x sales |
| Jan. | Celgene/Juno (cancer immunotherapies) | $9bn: $87 in cash per share (an 80% premium); 3.29x sales |
| Jan. | Celgene/Impact (cancer therapeutics) | $7bn: $1.1bn in cash up front, plus $5.9bn in potential earn-outs ($1.4bn related to regulatory milestones and $4.5bn related to tiered sales goals) |

*SOURCE: Strategic Transactions | Pharma Intelligence, 2018*

from its contracts with networks of retail, home delivery, and specialty pharmacies, which deliver drugs. The acquisition aims to improve medical and pharmacy benefits for patients and connections between providers and patients, and will offer expanded services and distribution channels. *(Also see "Cigna/Express Scripts: The End Of The Standalone PBM Era" - Scrip, 8 Mar, 2018.)* The combination will also help Express Scripts recoup some of the business it will lose following the December 2019 expiration of its contract with insurer **Anthem Inc.**, its largest customer, which will greatly reduce the number of lives the PBM manages. *(Also see "Express Scripts Combination With Cigna's PBM Could Reverse Deficit From Losing Anthem" - Pink Sheet, 8 Mar, 2018.)*

The consumer products industry saw some major consolidation during Q1, led by **GlaxoSmithKline PLC**'s $13 billion buyout of the 36.5% stake held by **Novartis AG** in their 2014 consumer health joint venture. At the time the JV was set up (concurrent with a separate asset swap in which GSK got Novartis' vaccines business and Novartis bought most of GSK's oncology operations), GSK held the majority ownership (63.5%). However, Novartis retained a put option requiring GSK to purchase its minority stake during the period starting March 2018 through March 2035, which GSK has now done. *(Also see "GSK Exercises Right To Buy Out Novartis Consumer Healthcare JV For $13bn" - Scrip, 27 Mar, 2018.)* The value of the assets represented by Novartis' stake is £5.9 billion ($8.3 billion), with an adjusted operating profit of £494 million. The deal enables Novartis to focus on core businesses and bolt-on acquisitions, while allowing GSK to better allocate its resources toward pharma R&D. *(Also see "GSK Gains Clarity For Pharma Focus Through Novartis Consumer JV Buy" - Scrip, 27 Mar, 2018.)*

In March, GSK withdrew from bidding proceedings to buy **Pfizer Inc.**'s consumer health business, which includes the *Advil*, *Robitussin*, and *Nexium* brands, although this segment represents just 6% of Pfizer's total sales. **Reckitt Benckiser Group PLC** was another potential suitor, but has also since dropped its bid. *(Also see "GSK And Reckitt Opting Out Of Pfizer's Consumer Business Sale Speaks Volumes" - Pink Sheet, 25 Mar, 2018.)* Pfizer is continuing to review alternatives for its OTC business, which is still on the block for as much as $20 billion, but some industry analysts believe a spin-off may be the best option and command a higher price than a divestiture to another firm. *(Also see "Pfizer Mum On Consumer Business Plans As Analysts Say Spin-off" - Pink Sheet, 1 Feb, 2018.)*

In another large consumer transaction, contract research organization (CRO) **Kolmar Korea Co.** agreed to acquire for $1.2 billion **CJ CheilJedang Corp.**'s **CJ Healthcare**, which manufactures OTC drugs and health foods; the diversified parent company is divesting the business to put more energies into its core food business. The CJ OTC unit brought in 2017 revenues of $466 million (for a 2.62x enterprise value to sales multiple) and also has a pipeline centered around digestive, musculoskeletal, liver, and immune diseases. The deal enables Kolmar to grow its pharma development operations and sales and distribution networks in South Korea. *(Also see "Kolmar Korea Eyes Pharma Expansion Via CJ*

*HealthCare Acquisition" - Scrip, 21 Feb, 2018.)* Kolmar wasn't the only CRO involved in a consumer health arrangement; in a March deal, private consumer dermatology company and contract development and manufacturing organization (CDMO) **BioMed Laboratories LLC** (topical skin, wound, and ostomy care products) was scooped up by diversified **Scapa Group PLC**'s US medical-focused division **Scapa Healthcare** for $32 million ($19 million up front and $13 million more in potential earn-outs).

**Celgene Corp.** was an active Q1 acquirer, commanding two spots on the Top 5 M&A list with separate billion-dollar-plus January acquisitions of cancer firms. First Celgene bought **Impact Biomedicines** for $1.1 billion initially, and up to $5.9 billion more in earn-outs related to regulatory and tiered sales goals achieved by Impact's sole candidate fedratinib, a selective JAK2 kinase inhibitor in Phase III for treatment-naïve myelofibrosis and also in Phase II for additional cancer indications. Impact expects an NDA submission in myelofibrosis by mid-year. *(Also see "Celgene's $1.1bn Impact Buy Is First Of More Deals To Come In 2018 And Beyond" - Scrip, 9 Jan, 2018.)*

Next Celgene purchased the remaining 90.3% of cellular immunotherapies developer **Juno Therapeutics Inc.** that it didn't already own for $87 per share, or approximately $9 billion. Celgene held a minority stake in the cancer-focused biotech through a 2015 alliance in which it optioned Juno's chimeric antigen receptor T-cell (CART) and T-cell receptor (TCR) projects. In 2016 Celgene exercised the option to develop and sell the CD19 program (outside of the US and China), and now with full control of Juno's pipeline, Celgene is most interested in JCAR017, currently in a Phase II pivotal trial for relapsed/refractory diffuse large B-cell lymphoma, with regulatory approval anticipated next year. Once approved, Juno estimates the compound could generate as much as $3 billion in sales. *(Also see "Celgene Seeks CAR-T Leadership, Hematology Diversification With Juno Buy" - Scrip, 22 Jan, 2018.)* A January 2018 Datamonitor Healthcare PharmaVitae report details how the transaction will propel Celgene into the expanding cellular immunotherapy space and boost its pipeline and long-term growth potential.

Another player that engaged in top M&A pacts during Q1 was **Sanofi**, also with two big January transactions, but Sanofi's dealings instead focused on growing its hematology business. *(Also see "Ablynx, Bioverativ Buys Drive Sanofi's Hematology Reign" - Scrip, 29 Jan, 2018.)*First it bought 2016 **Biogen Idec** spin-out **Bioverativ Inc.** (therapies for hemophilia and other rare blood disorders) for $11.4 billion. The Bioverativ buy grows the Big Pharma's blood disorder business, with the addition of half-life therapies *Eloctate* (recombinant Factor VIII) for hemophilia A and *Alprolix* (recombinant Factor IX) for hemophilia B. *(Also see "Sanofi Builds Blood Disorder Specialty With Bioverativ Buy" - Scrip, 22 Jan, 2018.)* In addition to hemophilia, Bioverativ has in its pipeline Phase III BIVV009 for cold agglutinin disease (which it gained through the acquisition of True North Therapeutics a few months after being spun off from Biogen), and earlier-stage projects for beta thalassemia and sickle cell disease. *(Also see "Bioverativ: More Than Just A Hemophilia Company" - Scrip, 22 Jan, 2018.)*

In a second transaction the following week, Sanofi outbid competing suitor **Novo Nordisk AS** for Belgian biotech **Ablynx NV**, paying €45 ($59.92; a 37% premium) per share up front, for an equity value of €3.8 billion ($5.1 billion), versus the best Novo offer of €28/share (a 46% premium) in cash up front, plus up to €2.50/share in CVRs, for an equity value of €2.3 billion ($2.7 billion). *(Also see "Novo Outbid As Sanofi Agrees €3.9bn Ablynx Acquisition" - Scrip, 29 Jan, 2018.)* Through Ablynx, Sanofi gains lead compound caplacizumab, an anti-vWF *Nanobody* awaiting approval in Europe (expected later this year) for the rare blood disease acquired thrombotic thrombocytopenic purpura (aTTP). US approval and launch is anticipated by the first half of 2019. In addition to caplacizumab, Sanofi gets a pipeline of over 45 in-house and partnered projects (eight of which are Nanobodies), including candidates for inflammation, oncology, and respiratory diseases.

Big Pharma didn't have a large M&A presence during 2017, with only eight completed deals (for an aggregate $33 billion), but so far 2018's opening month has already featured five Big Pharma M&As, together valued at more than $30.5 billion, perhaps prompted by tax reform. (*See Exhibit 4.*) Although no value was disclosed, there was also a divestiture in which **AstraZeneca PLC**'s **MedImmune LLC** division spun off a new company, **Viela Bio**, responsible for developing three preclinical and three clinical-stage compounds in non-core areas, including anti-CD19 monoclonal antibody inebilizumab, in Phase II for neuromyelitis optica. *(Also see*

**Exhibit 4: Big Pharma Starts Off 2018 With Strong M&A Activity**

| Date | Big Pharma Acquirer/Target (Business) | Deal Value ($m) |
|---|---|---|
| Mar. | GSK/Novartis' stake in 2014 JV (consumer health) | 13,000 |
| Jan. | Sanofi/Bioverativ (therapies for hemophilia and other rare blood disorders) | 11,400 |
| Jan. | Sanofi/Ablynx (Nanobody therapeutic proteins for inflammation, hematology, oncology, and respiratory diseases) | 5,100 |
| Jan. | Takeda/TiGenix (regenerative medicines for anti-inflammatory conditions) | 621 |
| Feb. | Merck/Viralytics (oncolytic immunotherapies) | 394 |

*SOURCE: Strategic Transactions | Pharma Intelligence, 2018*

*"AstraZeneca Keeps R&D Focus, Spins Out Phase II Neuromyelitis Optica MAb Into New Biotech" - Scrip, 28 Feb, 2018.)*

**Takeda Pharmaceutical Co. Ltd.** agreed to acquire the remaining shares of regenerative medicine partner **TiGenix NV** that it does not already own for €517 million ($621 million) In 2016, Takeda took a 4% equity stake in the company when it licensed exclusive ex-US rights to TiGenix's stem-cell based Cx601 (*Alofisel* (darvadstrocel)), since approved in Europe for Crohn's disease.

Merck & Co.'s buy of immune-oncology partner **Viralytics Ltd.** at $1.38/share (a 165% premium) shows the firm's commitment to boost its pipeline through M&A and expands their 2015 trial collaboration evaluating Viralytics' *Cavatak* oncolytic immunotherapy (a proprietary formulation of the Coxsackievirus Type A21 that preferentially infects and kills cancer cells) together with Merck's PD-1 antagonist *Keytruda* (pembrolizumab). Building up IO combinations will be key in the wake of the early April 2018 announcement of the Phase III failure of the Big Pharma's combination of Keytruda with **Incyte Corp.**'s IDO inhibitor epacadostat in first-line metastatic melanoma. *(Also see "Incyte/Merck's ECHO-301 Failure Casts More Shadow On IDO Space" - Scrip, 6 Apr, 2018.)*

## Alliances

Biopharma alliance activity in Q1 featured 100 alliances, less than the 122 announced in 2017's final quarter. At a total value of $30.7 billion, however, Q1 clearly beat the $22.6 billion from the previous quarter.

Exactly ten first-quarter deals reached or surpassed the billion-dollar mark, led by immuno-oncology partnerships between Merck & Co. and **Eisai Co. Ltd.**and **Bristol-Myers Squibb Co.** and **Nektar Therapeutics**. (*See Exhibit 5.*) Immuno-oncology agreements such as these have tended to draw top dollar in recent years. But what makes these two stand out in particular is that both partnerships formalize deals following clinical trial collaborations previously signed.

Merck and Eisai have been studying different combinations of their therapies since 2015, including Merck's PD-1 antagonist *Keytruda* (pembrolizumab) with Eisai's *Lenvima* (lenvatinib) or *Halaven* (eribulin) in endometrial cancer and metastatic triple-negative breast cancer, respectively. Their new agreement, worth $5.8 billion (including a $1.85 billion up-front fee in cash and equity, the largest of the quarter), builds upon their initial work with studies of the Keytruda/Lenvima combination in 11 indications across six cancer types. They will also conduct a basket trial for multiple cancers. As a result, Merck and Eisai have formalized their collaboration with deal-like terms, including outlining co-development rights, the booking of sales, and cost/profit share. *(Also see "Eisai And Merck & Co Supercharge Lenvima's Potential" - Scrip, 8 Mar, 2018.)* Merck separately signed another clinical trial collaboration in Q1, agreeing to combine Keytruda with **PharmAbcine Inc.**'s TTAC0001 (tanibirumab), a Phase II anti-VEGFR2 monoclonal antibody, in recurrent glioblastoma multiforme and metastatic triple-negative breast cancer.

Similarly, BMS and Nektar initially got together in 2016 to study a combination of the former's PD-1 antagonist *Opdivo* (nivolumab) and the latter's CD122-biased immunocytokine therapy/IL-2 agonist NKTR214 in five tumor types. Not only does the new deal expand the number of cancers being investigated to more than 20 indications across nine tumor types, it also outlines an official development plan with shared commercial rights, costs splits, and financial terms. Altogether, Nektar could receive up to $3.6 billion in up-front and milestone payments. In addition to continuing to study Opdivo and NKTR214, they will also evaluate an Opdivo+*Yervoy* (ipilimumab) and NKTR214 combo. *(Also see "Nektar/Bristol Deal May Shake Up Immuno-Oncology Landscape" - Scrip, 14 Feb, 2018.)* BMS turned out to be quite busy during the first quarter. It also received options on microbiome programs developed using **Sirenas LLC**'s *Atlantis* artificial intelligence system, and got nonexclusive rights to **Domain Therapeutics SA**'s *bioSens-All* GPCR discovery platform.

A key theme throughout Q1's billion-dollar pacts was neurodegenerative diseases. (*See Exhibit 6.*) Exactly half of the top ten deals were focused on that area, led by a multi-year $2.2 billion deal between **Celgene Corp.** and **Prothena Corp. PLC**. Celgene may exercise options on three targets – tau, TDP-43, and an undisclosed one – upon IND filing, and drug candidates may be developed for multiple diseases, including Alzheimer's disease (AD), progressive supranuclear palsy, fronotemporal dementia and other tauopathies, and amyotrophic lateral sclerosis. *(Also see "Celgene Further Commits To Neuroscience With Prothena Pact " - Scrip, 21 Mar, 2018.)* Celgene is currently heavily involved in oncology and immunology/inflammation, but is looking to diversify into other therapy areas, such as CNS conditions. During Q1, the company also received exclusive worldwide rights to **Abide Therapeutics Inc.**'s epilepsy compound ABX1772, and is working with **Vividion Therapeutics Inc.**'s proteomics technology to discover candidates across several indications, including neurology.

Takeda was involved in two big CNS deals. In partnership with **Wave Life Sciences Ltd.**, Takeda has the option to co-develop and commercialize oligonucleotides for Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and spinocerebellar ataxia type 3. In addition, Takeda gets exclusive rights to preclinical projects in AD, Parkinson's, and other CNS diseases. Wave Life will get $170 million up front, $60 million in

**Exhibit 5: Top Biopharma Alliances, Q1 2018**

| Month | Licensee/ Licenser | Deal Subject(s) | Potential Deal Value* ($m) |
|---|---|---|---|
| Mar. | Merck & Co./Eisai | Co-development and co-commercialization of Eisai's Lenvima (lenvatinib) as a monotherapy and combination with Merck & Co.'s Keytruda (pembrolizumab) | 5,755 |
| Feb. | Bristol-Myers Squibb/Nektar | Co-development and co-commercialization of Nektar's NKTR214 in combination with BMS's Opdivo (nivolumab) and Opdivo + Yervoy (ipilimumab) | 3,630 |
| Feb. | Gilead and Kite Pharma/Sangamo | Zinc finger nuclease gene editing technology for the development of T-cell and natural killer cell therapies | 3,160 |
| Mar. | Celgene/Prothena | Options on programs targeting tau, TDP-43, and an undisclosed target in neurodegenerative diseases including Alzheimer's, progressive supranuclear palsy, fronotemporal dementia and other tauopathies, and amyotrophic lateral sclerosis | 2,242 |
| Feb. | Takeda/Wave Life Sciences | Options on four nucleic acid therapies for Huntington's disease, ALS, frontotemporal dementia, and spinocerebellar ataxia type 3; plus exclusive rights on up to six preclinical candidates for CNS diseases, including Alzheimer's and Parkinson's | 2,230 |

**Potential deal value is the sum of up-front fees/equity plus pre- and post-commercialization money.*
*SOURCE: Strategic Transactions | Pharma Intelligence, 2018*

**Exhibit 6: Billion-Dollar Deals Focus On Neurodegenerative Disease, Q1 2018**

| Date | Licensee/ Licenser | Compounds/Products | Potential Deal Value* ($m) |
|---|---|---|---|
| Mar. | Celgene/ Prothena | Three preclinical projects against tau, TDP-43, and an undisclosed target for potentially Alzheimer's disease, progressive supranuclear palsy, fronotemporal dementia, and other tauopathies, and amyotrophic lateral sclerosis | 2,242 |
| Feb. | Takeda/Wave Life Sciences | Phase Ib/IIa gene expression inhibitors WVE120101 and WVE120102 for Huntington's disease; preclinical C9ORF72-targeting WVE397201 for ALS and frontotemporal dementia; candidate targeting the ATXN3 gene for spinocerebellar ataxia type 3; up to six preclinical candidates in development for CNS diseases, including AD and Parkinson's | 2,230 |
| Mar. | Akcea/Ionis | Phase III inotersen (ISIS420915) for hereditary transthyretin amyloidosis (ATTR); preclinical AKCEA-TTR-LRx for hereditary and wild-type forms of ATTR | 1,880 |
| Feb. | AbbVie/ Voyager | Gene therapies that express tau antibodies for treating neurodegenerative conditions including Alzheimer's disease, progressive supranuclear palsy, and frontotemporal dementia. | 1,179 |
| Jan. | Takeda/ Denali | Preclinical Alzheimer's candidates ATV: BACE1/Tau (secretase beta and tau aggregation inhibitor) and ATV: TREM2 (TREM2 antagonist), and a third undisclosed discovery-stage compound | 1,172 |

**Potential deal value is the sum of up-front fees/equity plus pre- and post-commercialization money.*
*SOURCE: Strategic Transactions | Pharma Intelligence, 2018*

R&D funding and reimbursement, and potentially $2 billion in milestones. *(Also see "Takeda Catches Rising Tide Of Antisense Neuroscience R&D" - Scrip, 21 Feb, 2018.)* In another option-based deal (worth $1.2 billion), Takeda teamed up with **Denali Therapeutics Inc.** on three early-stage programs, including two in AD, based on Denali's blood-brain barrier (BBB) delivery platform called *ATV* (*Antibody Transport Vehicle*) . Through a separate Q1 alliance, Denali's efforts in engineering biologics to cross the BBB are being furthered through custom cell-line development and formulation and dosage form technologies from **Lonza Group Ltd.**

Rounding out the billion-dollar partnerships in the neurology area were in-licensing agreements by **Akcea Therapeutics Inc.** and **AbbVie Inc.** Akcea received from its parent **Ionis Pharmaceuticals Inc.** exclusive global rights to the antisense therapies inotersen (in pre-registration) and AKCEA-TTR-LRx (preclinical), both in development for hereditary transthyretin amyloidosis. In all, Ionis could receive up to $1.9 billion, plus royalties. Inotersen had been optioned to GlaxoSmithKline in 2010, but the Big Pharma turned it down in mid-2017 because of a pipeline reprioritization. In their $1.2 billion agreement, AbbVie and **Voyager Therapeutics Inc.** will work on one-time gene therapies – delivered to the brain via AAV vectors – that produce anti-tau antibodies for the treatment of neurodegenerative diseases, including AD, progressive supranuclear palsy, and frontotemporal dementia. *(Also see "AbbVie's Alzheimer's Efforts Voyage Into AAV-Targeted Tau Antibodies" - Scrip, 20 Feb, 2018.)*

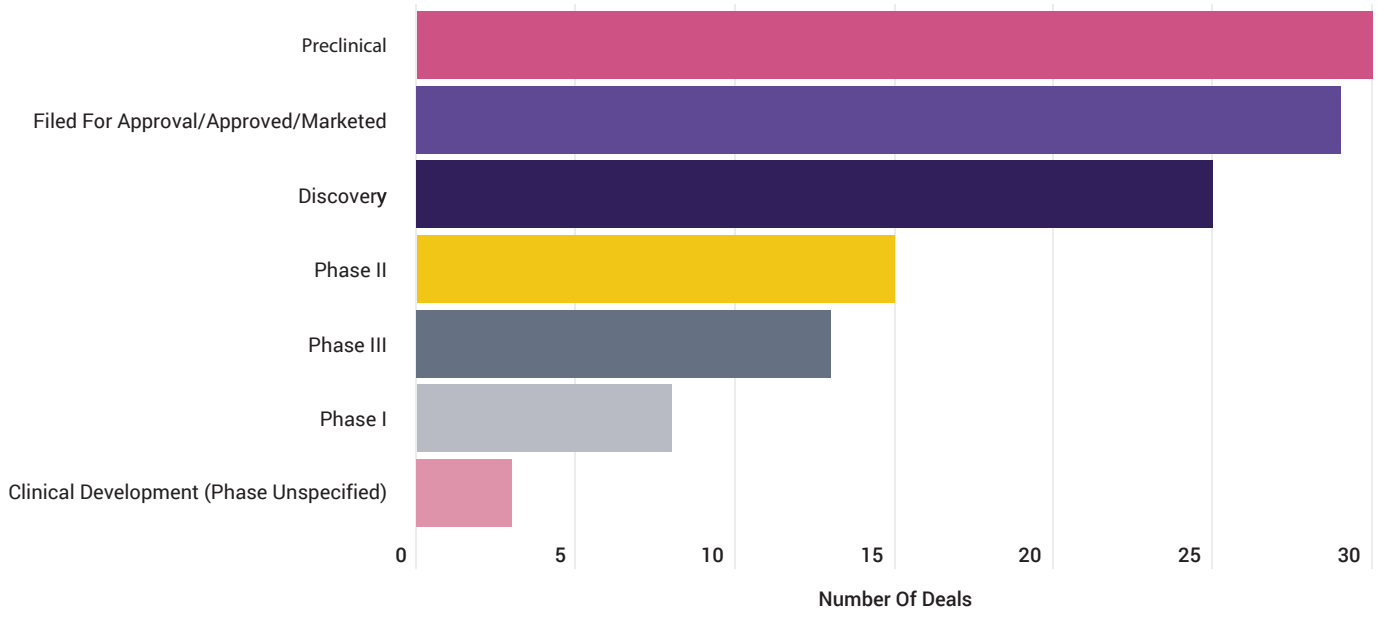
After its acquisition of **Kite Pharma Inc.** in 2017 and Kite's approved CART therapy *Yescarta* (axicabtagene ciloleucel), **Gilead Sciences Inc.** stated that the deal would allow it to build out an entire oncology platform focused on cell and gene therapies. *(Also see "Gilead Makes Cell Therapy The Base Of Its Oncology Platform With Kite Buy" - Scrip, 29 Aug, 2017.)* Gilead has followed through with that pledge, since buying **Cell Design Labs Inc.**, a former Kite investment, in 2017, and in Q1 2018 signing a $3.2 billion gene editing deal with **Sangamo Therapeutics Inc.**, a pioneer in zinc finger nuclease editing technology. Together, the companies plan to modify both T-cells and natural killer

cells to express chimeric antigen receptor as well as other proteins. The resulting allogeneic or autologous therapies are expected to treat undisclosed cancers. *(Also see "Gilead Partners With Sangamo For Gene Editing As It Builds Up Kite's Cell Therapy Platform" - Scrip, 22 Feb, 2018.)* Kite/Gilead additionally penned a clinical trial collaboration with Pfizer to study a combination of Yescarta and Pfizer's 4-1BB (CD137) agonist utomilumab in refractory large B-cell lymphoma. Separately during Q1, Sangamo also turned to long-time collaborator Pfizer in a new gene editing deal, focused on C9ORF72 gene mutations which cause amyotrophic lateral sclerosis and frontotemporal lobar degeneration. Partners since at least 1998, the companies most recently teamed up in 2017 to develop SB525, now in Phase II for hemophilia A.

Two key deals of the quarter focused on biosimilars development. **Sandoz International GMBH**, a division of Novartis, signed a broad collaboration with **Biocon Ltd.** covering immunology and oncology biosimilars. The companies will split commercialization rights, with Sandoz in charge of sales in North America and the EU, and Biocon in the rest of the world. The agreement is significant in that Biocon, which has traditionally taken on more of a manufacturing role in biosimilars, will now gain some commercial experience. *(Also see "Riding The Next Wave Of Biosimilars: Sandoz To Link Up With India's Biocon" - Scrip, 18 Jan, 2018.)* While the value of the Sandoz/Biocon alliance was not disclosed, **Mylan NV** and **Revance Therapeutics Inc.** announced a $350 million deal to produce a short-acting biosimilar version of *Botox* (onabotulinumtoxinA). A blockbuster for **Allergan Inc.**, Botox is a neuromodular that is used for multiple indications, including pain and aesthetics. Mylan will have exclusive worldwide rights to the biosimilar, except in Japan. *(Also see "Mylan Set To Develop Biosimilar Botox In Deal With Revance" - Scrip, 28 Feb, 2018.)*

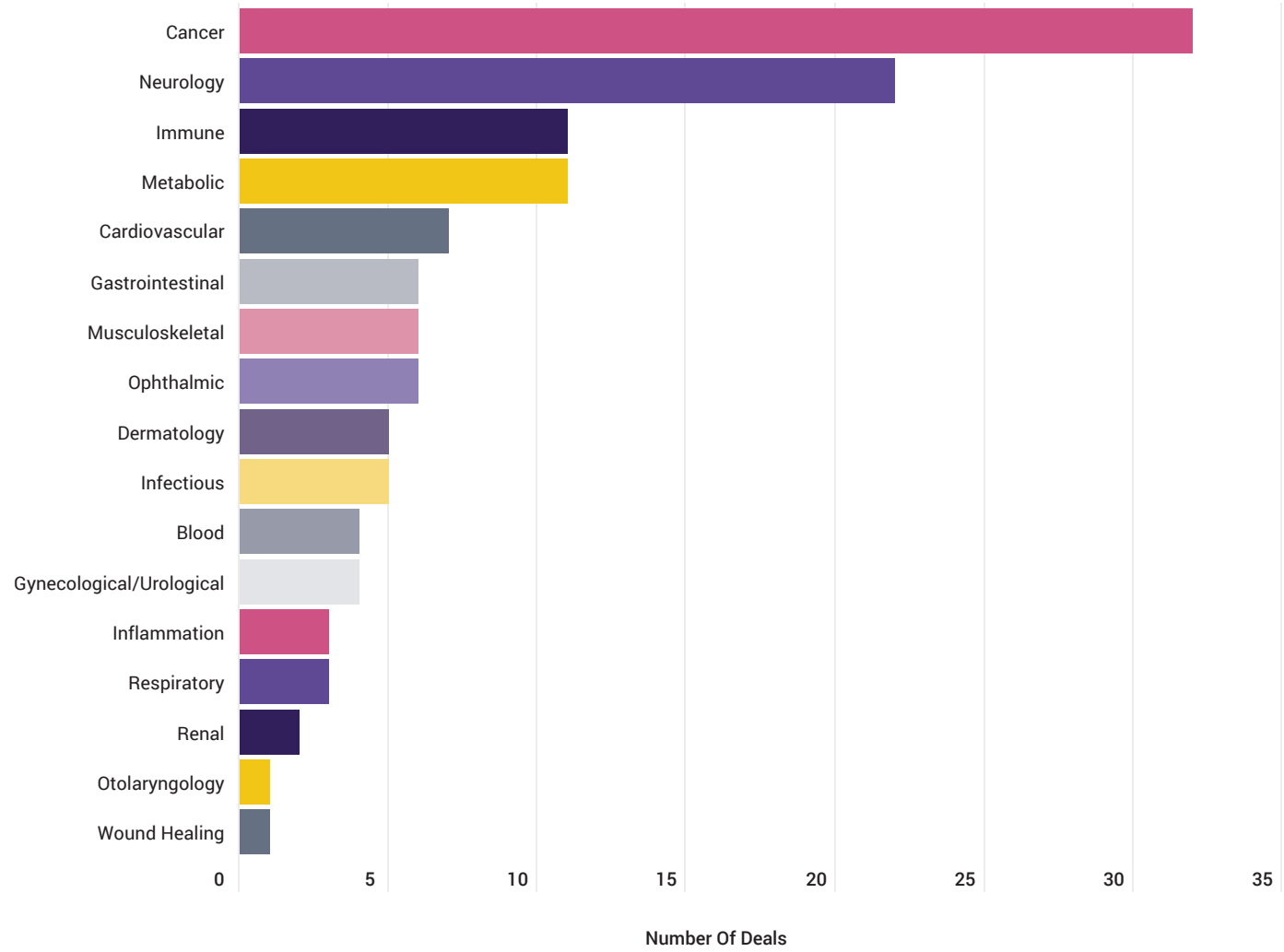
Preclinical deals proved to be the most popular alliances targets of the quarter, but not by a large margin. There was only a one deal difference compared with licensing agreements for approved drugs. Still, discovery-stage alliances rounded out the top three phases. (*See Exhibit 7.*) And the focus on oncology and neurology assets in the top valued deals was not surprising given these were the areas where most of the deal volume was concentrated in Q1. Tying for third place were alliances involving licenses for immunology and metabolic programs. (*See Exhibit 8.*)

**Exhibit 7: Q1 2018 Alliances By Phase**




*Note: Deals may be counted more than once if multiple phases are involved.*
*SOURCE: Strategic Transactions | Pharma Intelligence, 2018*

## Exhibit 8: Q1 2018 Partnerships By Therapeutic Area




*Note: Deals may be counted more than once if multiple therapeutic areas are involved.*
*SOURCE: Strategic Transactions | Pharma Intelligence, 2018*

Specialised Therapeutics®

## HOW THE DEAL WAS DONE:

# Specialised Therapeutics' CEO Carlo Montagner Discusses A Recent Partnership Deal To Commercialize Nerlynx™ (Neratinib)

**Headquartered in Singapore, Specialised Therapeutics is an international, independent pharmaceutical company commercializing novel specialist medicines to patients in Australia, New Zealand and South East Asia. Founded in 2008 by international pharmaceutical executives Carlo Montagner and Bozena Zembrzuski, Specialised Therapeutics (ST) began with a single oncology product that is now one of the most successful branded chemotherapies ever commercialized in Australia. Since its inception, the ST product portfolio has rapidly expanded, now incorporating specialist oncology, haematology, supportive care and ophthalmology products, as well as genomic assays. ST's successful business strategy has always been to partner with international biotechs and champion their products from pre-registration to full commercialization.**

"Our most recent partnership deal was with US-based Puma Biotechnology (NASDAQ:PBYI)," said Carlo Montagner, CEO, Specialised Therapeutics.

This novel early breast cancer drug first came to our attention in 2011 when Puma acquired the rights from Pfizer.

Following a successful FDA ODAC hearing in 2017, we reached out to Puma for an initial exploratory discussion on commercializing NERLYNX in our region. Less than 6 months later, we not only struck an exclusive license agreement, but we have submitted the New Drug Application dossier to the Therapeutic Goods Administration (TGA) and have made NERLYNX available to appropriate Australian patients via a strictly-controlled patient access program using our proprietary access program platform.

We were able to move quickly because, I am 100% owner and CEO of the company, our internal review and approval processes are not subject to multiple internal senior management and board reviews.

If we make a commitment to filing a dossier on a particular date – subject to external influences beyond our control – we have always achieved that commitment.

We were looking for a drug that fulfilled an unmet need and provided a reasonable commercial opportunity.

NERLYNX overwhelmingly met these criteria. It is the first FDA-approved drug for extended adjuvant therapy in women with early stage HER2+ breast cancer and is clearly not a 'me-too' product.

In this case, due diligence processes were also expedited. Our team of senior pharma executives was able to rapidly assess the commercial opportunity.

Like all our agreements, the Puma deal was tailored to meet the needs of our partner.

Making NERLYNX available to women prior to TGA approval has required particular commercialization skill.

In addition to the usual advisory boards and meeting with key stakeholders, ST also launches early access programs to potential prescribers.

These programs ensure our customers become familiar with the product, but more importantly, they enable appropriate access to patients in need at the earliest opportunity.

Our NERLYNX access program was launched in Australia in late March – four months post-deal.

We have developed a rigorous process for managing these access programs pre- and post regulatory approval, and are currently operating several simultaneously.

With NERLYNX, we are targeting a reimbursement approval within 18 months of submitting our regulatory dossier.

We have a strong track record of achieving these critical milestones and now look forward to making this important medicine available to appropriate Australian women."

# Big Pharma Presence In Gene Therapy Dealmaking Validates Technology

▶ By Amanda Micklus

A robust deal-making market within the last several years has enabled gene therapy drug development to be adequately funded and advanced through the clinic.

Early research and development in gene therapy has been pioneered by smaller biotech companies, many of which have been able to further their work by partnering, or even acquiring, each other. While this peer-to-peer dealmaking has certainly continued, Big Pharma and other large pharmaceutical firms have jumped on board, and through their investments and more importantly their financial resources and marketing expertise, are looking to translate these discoveries into viable commercial products.

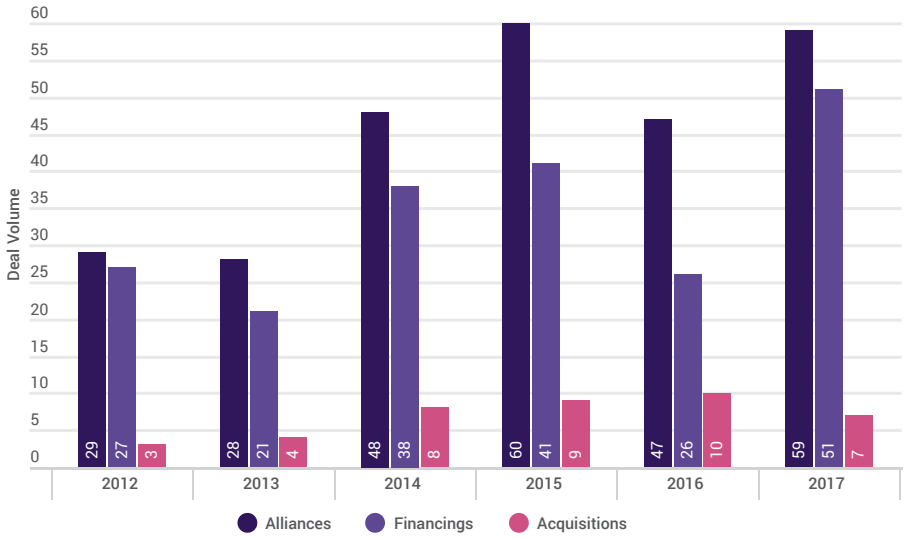
Between 2012 and 2017 (through October), gene therapy was the subject of 516 deals across various types of transactions, including financings, alliances, and full company acquisitions. (*See Exhibit 1.*) Most of the activity was done through partnerships, which allow companies to devise licensing agreements around a single gene therapy asset or even multiple products or technologies. Such partnerships represented 52% of the total deal volume over the time period. Alliances may be more straightforward to arrange than acquisitions, which are financially more complex and may take longer to construct than a simpler licensing agreement.

Several Big Pharma and mid-sized pharma companies have become active gene therapy in-licensers. Based on the focus of the gene therapy approach – whether it is "cell and gene" therapy/ex vivo therapy, or gene therapy/in vivo therapy, it's possible to get a sense for where future deals may be concentrated. (*See Exhibit 2.*) With the highest volume, **Novartis AG** has accumulated a strong collection of alliances in the cell and gene therapy market. Notably, in 2012 the company in-licensed CAR-T technologies from the **University of Pennsylvania**, culminating in the development and approval of the first CAR-T therapy in the US, *Kymriah* (tisagenlecleucel-t), in 2017. To secure the stable manufacturing of Kymriah, Novartis has in-licensed non-exclusive rights to lentiviral vectors from both **Oxford BioMedica PLC** (through a $190 million deal) and **bluebird bio Inc.**, and has also been building up its intellectual property portfolio with licenses to **Celyad SA**'s CAR-T patents. In addition, Novartis made an investment in gene editing, signing a five-year agreement with **Intellia Therapeutics Inc.** in 2015 to apply CRISPR/Cas9 to CAR-T therapies. While these agreements show Novartis aims to be a leader in ex vivo therapy, the company also seems to be broadening its overall footprint in the gene therapy market and establishing a presence in in vivo therapy: in early 2018, Novartis received ex-US rights to **Spark Therapeutics Inc.**'s *Luxturna* (voretigene neparvovec), approved in the US in 2017 for confirmed biallelic RPE65 mutation-associated retinal dystrophy.

There are other large pharma companies that have done multiple gene therapy alliances between 2012 and 2017, including **Pfizer Inc.**, **Biogen Inc.**, **Johnson & Johnson**, **Celgene Corp.**, **Astellas Pharma Inc.**, and **Sanofi**. Aggregated alliances by some firms have covered a mixture of both gene therapy and cell and gene therapy. There are others, though, that are solely doing deals in one approach as opposed to the other. For instance, all of Celgene and **GlaxoSmithKline PLC**'s alliances concentrate on cell and gene therapy, where these companies have dedicated large amounts of resources and funding. On the other hand, Biogen and Sanofi, for example, have concentrated more on in vivo gene therapy.

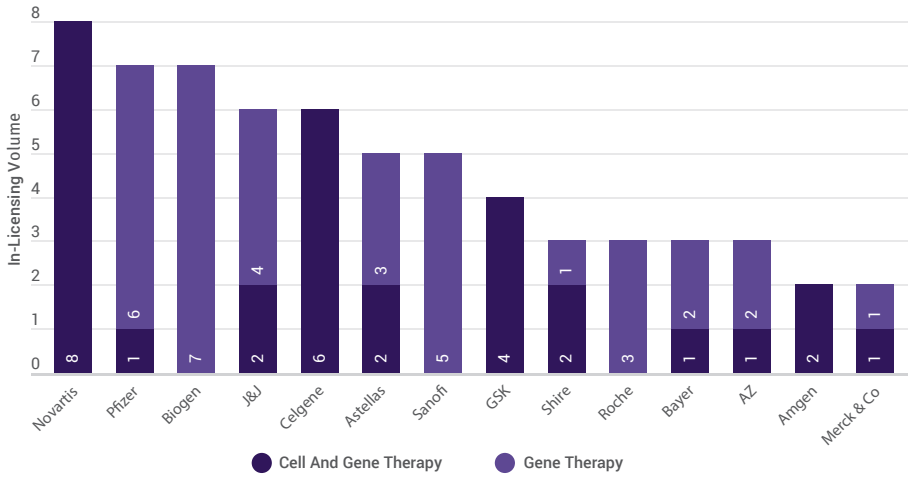
Among the top 10 gene therapy alliances by total potential value, Pfizer led with its $2.9 billion agreement signed in 2014 with **Cellectis SA**. Their deal involves 27 CAR-T therapy targets combined from both partners, with Pfizer holding exclusive development and commercialization rights to programs involving its targets, and a right of first refusal on Cellectis' targets. The most advanced candidate, UCART19 (sublicensed from **Servier SA**, which has a separate option agreement with Cellectis), is an allogeneic treatment that become the first such off-the-shelf product to start a US clinical trial when it began Phase I in July 2017. *(Also see "Cellectis Moves First Off-The-Shelf CAR-T Into US Clinical Trials" - Scrip, 3 Jul, 2017.)* It's being tested in various stages for chronic lymphocytic leukemia, acute lymphocytic leukemia, and diffuse large B-cell lymphoma.

## Exhibit 1: Gene Therapy Deals By Volume And Deal Type, 2012–17




*Note: 2017 data through October*
*Sources: Medtrack; Strategic Transactions | Pharma Intelligence, 2018*

## Exhibit 2: Big Pharma And Mid Pharma Gene Therapy In-Licensing Volume By Category, 2012–17




*Note: 2017 data through October. Cell and gene therapy = ex vivo, and gene therapy = in vivo.*
*Sources: Medtrack; Strategic Transactions | Pharma Intelligence, 2018*

While full-company acquisitions in gene therapy are fewer and far between – they have only accounted for 8% of the volume over the past five-and-a-half years – Big Pharma and other large firms have done some of the biggest deals. The only billion-dollar gene therapy acquisitions have been signed by **Shire PLC** and**Gilead Sciences Inc.**, and those were valued in the multi-billion range. The result of an unsolicited bid, Shire purchased **Baxalta Inc.** in 2015 and gained SHP654, a factor VIII gene therapy for hemophilia A. In addition, after the takeover by Shire, Baxalta went on to sign a CAR-T therapy alliance with **Precision BioSciences Inc.**. The second-largest biotech acquisition overall in 2017 (behind Johnson & Johnson/**Actelion Pharmaceuticals Ltd.** at $30 billion), Gilead and **Kite Pharma Inc.**'s $12 billion deal further validates the interest of large pharma corporations in the CAR-T therapy field. Shortly after Gilead's take-

over was announced, the FDA approved *Yescarta* (axicabtagene ciloleucel), the second CAR-T therapy cleared by the FDA in 2017 (following Novartis' Kymriah).

At $645 million, Pfizer's acquisition of **Bamboo Therapeutics Inc.** ranked third in value, behind Shire/Baxalta and Gilead/Kite Pharma, in the top ten acquisitions done. (*See Exhibit 3.*) In early 2016, Pfizer had bought a 22% stake in Bamboo, which is using recombinant adeno-associated virus vectors to develop treatments for neuromuscular diseases. Its lead candidate is now in Phase II for giant axonal neuropathy. In late 2016, Pfizer acquired the remaining ownership stake in Bamboo for $150 million up front and up to $495 million in development, regulatory, and commercial earn-outs linked to milestones of Bamboo's key programs.

**Exhibit 3: Top 10 Gene Therapy Acquisitions By Value, 2012–17**

| Date | Category | Acquirer | Target | Target Focus In Gene Therapy | Upfront Payment ($m) | Earn-Out ($m) | Total Value ($m) |
|---|---|---|---|---|---|---|---|
| August 2015 | Gene therapy | Shire | Baxalta | Factor VIII therapy SHP654 for hemophilia A | 32,000 | n/a | 32,000 |
| August 2017 | Cell and gene therapy | Gilead | Kite Pharma | CAR-T therapy | 11,900 | n/a | 11,900 |
| August 2016 | Gene therapy | Pfizer | Bamboo Therapeutics | Recombinant adeno-associated virus vector therapies for neuromuscular diseases | 150 | 495 | 645 |
| April 2014 | Gene therapy | Baxter | Chatham Therapeutics | BAX335 for hemophilia B | 70 | 560 | 630 |
| August 2017 | Cell and gene therapy | CSL | Calimmune | Ex vivo hematopoietic cell gene therapies | 91 | 325 | 416 |
| May 2013 | Gene therapy | GlaxoSmithKline | Okairos | Viral vector gene delivery | 325 | n/a | 325 |
| March 2015 | Cell and gene therapy | Kite Pharma | T-Cell Factory | TCR cloning technology to discover, characterize, and select tumor-specific TCRs that can be used to genetically engineer T-cells used in gene therapies for cancer | 21 | 230 | 251 |
| May 2015 | Cell and gene therapy | Juno Therapeutics | Stage Cell Therapeutics | Isolation and expansion technologies for T-cells | 81 | 151 | 232 |
| January 2015 | Cell and gene therapy | Cardio3 BioSciences | OnCyte | CAR-T therapy candidate using natural killer cell receptor | 10 | 172 | 182 |
| June 2014 | Cell and gene therapy | bluebird bio | Precision Genome Engineering | TrueCut homing endonuclease and MegaTAL-based gene editing | 24 | 135 | 159 |

*Notes: 2017 data through October. The "Category" column denotes approach, with cell and gene therapy = ex vivo, and gene therapy = in vivo. Following Shire's acquisition of Baxalta, which spun off from Baxter, Shire terminated development of BAX335.*

*Sources: Medtrack; Strategic Transactions | Pharma Intelligence, 2018*

***Editor's note: This article is adapted from Datamonitor Healthcare's February 2018 report, "Gene Therapy Deal-Making Trends, 2012–17."***

# $1.6bn ARMO Buy Gives Lilly Its Most Advanced Immuno-Oncology Asset

▶ By Mandy Jackson

**Eli Lilly & Co.** is behind its big pharma peers in terms of investments in immuno-oncology, although cancer drugs already are an important part of its portfolio, but now it's catching up with the IO fervor via the $1.6bn acquisition of **Armo BioSciences Inc.**

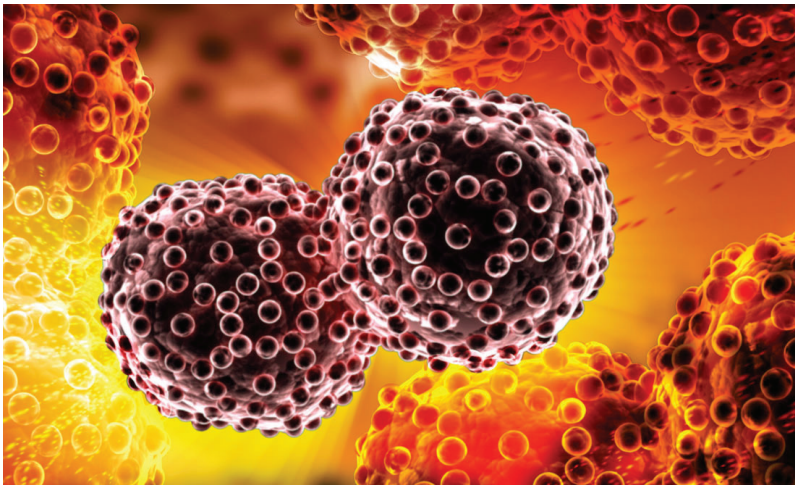
The Armo deal gives Lilly its most advanced immuno-oncology (IO) asset – the pegylated Interleukin-10 (IL-10) known as pegilodecakin (AM0010), which is a next-generation IO drug that may work well alone and in combination with first-generation immunotherapies. Lilly Oncology Senior Vice President, Global Development and Medical Affairs, Levi Garraway spoke with *Scrip* on May 10, the day the deal was announced, about how pegilodecakin fits into the company's broader oncology portfolio.

"Bringing in this particular asset, pegilodecakin, would bring one that is farthest along in clinical trials, but we do have several other IO assets in our pipeline," Garraway said.

"We brought it in because we felt that the mechanism of action was distinct and we saw that it had single-agent activity in some tumor types, but we do think that the biggest opportunity will likely be in combination," he added. "Combinations could include existing immune checkpoint inhibitors, but it will also include novel agents, and we do have some ideas about novel combinations using other [Lilly] portfolio drugs."

Lilly has its own PD-L1 inhibitor, LY3300054, in Phase I for the treatment of solid tumors, but the company lags behind leaders in the IO space, like **Merck & Co. Inc.** and **Bristol-Myers Squibb Co.**, which had the first PD-1 inhibitors approved in the US – *Keytruda* (pembrolizumab) and *Opdivo* (nivolumab), respectively.

Lilly also has early-stage immuno-oncology programs in the clinic targeting CSF-1R, TIM3 and IDO, and its preclinical alliances in the IO space include a collaboration involving Immunocore's T-cell receptor-based therapeutics and a



cancer vaccine agreement with CureVac. *(Also see "Immunocore attracts Lilly in co-co deal " - Scrip, 16 Jul, 2014.)* and *(Also see "Lilly's Billion-Dollar Deal With CureVac For 'Next Generation' Immunotherapies" - Scrip, 19 Oct, 2017.)*

> **"Our goal is to accelerate assets that are already in development, but also to augment the pipeline with multiple additional assets" – Lilly Oncology SVP Levi Garraway**

However, Garraway notes that the company still is focused on oncology generally, not just IO, within its cancer drug portfolio.

"We are interested in building out our entire Lilly Oncology pipeline. Our goal is to accelerate assets that are already in development, but also to augment the pipeline with multiple additional assets. Some of them, of course, will come from our research labs, but others will come from external opportunities, such as the Armo Biosciences opportunity, and it's not limited only to IO," he said.

## Investors Support Aggressive IO Expansion

Lilly agreed to pay $50 per share for Armo – a 67.7% premium over the newly-public biotechnology firm's May 9 closing stock price of $29.82. Armo closed up 67% at $49.80 after the all-cash transaction was announced. Shareholders who've owned the stock since Armo's initial public offering in January at $17 per share will have nearly tripled their investment when the acquisition closes; the companies expect to complete the transaction during the current quarter. *(Also see "IPO Update: Seven In January As Big Returns, Solid's Slip-Up Contribute To Bubble Concerns" - , 2 Feb, 2018.)*

"Given the company's IPO occurred in January, this is one of the fastest post-IPO exits we've seen in a long time," Jefferies analyst Biren Amin said in a May 10 note. "We believe the terms are fair given Armo has presented Phase I/II data on pegilodecakin in pancreatic cancer, non-small cell lung cancer (NSCLC), renal cell cancer (RCC) and metastatic melanoma."

"Armo is currently running the Phase III SEQUIOA trial in second-line pancreatic cancer with the first efficacy interim analysis expected in 2020," Amin added. "The company also recently initiated [a] Phase IIb trial in combination with anti-PD-1 in first- and second-line NSCLC in the respective CYPRESS-1 and -2 studies, which are expected to complete in 2019. Furthermore, we think Lilly could potentially evaluate pegilodecakin in RCC and additional tumor types."

CYPRESS-1 combines pegilodecakin with Merck's Keytruda, while the IL-10 is being evaluated in combination with Bristol's Opdivo in CYPRESS-2.

"We believe [pegilodecakin] in NSCLC is the main motivator for the acquisition given the large market opportunity, modeling about $1bn risk-adjusted peak sales opportunity in the first-line setting alone by our estimate," BMO Capital Markets analyst Matthew Luchini wrote on May 10.

Lilly investors endorsed the Armo deal, sending the pharma's stock 2% higher to close at $80.86.

"Our initial impression of Lilly's Armo acquisition is incrementally positive as it meaningfully improves Lilly's oncology franchise and improves the probability of Lilly becoming a viable competitor in the increasingly fragmented IO market," BMO's Alex Arfaei said in a May 10 note.

"The acquisition also gives Lilly other IO assets, including a pre-clinical anti-PD-1 (AM0001) and a LAG-3, which create the interesting possibility of internal wholly owned IO combos," Arfaei wrote.

Pegilodecakin is Armo's only clinical asset, but the company lists AM0001 and the pegylated IL-15 AM0015 as being in the pre-investigational new drug (IND) application stage. The pegylated IL-12 AM0012 and the LAG-3 inhibitor AM0003 are preclinical.

"Our near-term focus is realizing the near-term opportunities for [pegilodecakin], but there are several preclinical assets that will deserve attention and testing in the clinic as well," Garraway said.

## Investing In Lilly's Longer-Term Strategy

Morgan Stanley analyst David Risinger said in a May 10 note that Lilly has been taking steps recently to boost its immuno-oncology portfolio and its in-house expertise.

> **"Strategically, we understand we need to be active externally, and you can count on us to continue to look at all available choices to add to our pipeline, in particular, in oncology." – Lilly CEO David Ricks**

"Lilly's interest in IO was highlighted by its recent hiring of Leena Gandhi, director of thoracic medical oncology at NYU Perlmutter Cancer Center. Dr. Gandhi most recently served as the lead investigator on Merck's KEYNOTE-189 study," Risinger wrote. *(Also see "Merck's Keytruda Enjoys Clean Sweep In Lung Cancer, At Bristol's Expense" - Scrip, 17 Apr, 2018.)*

In general, the company has committed to bringing in more external programs, while still developing most of its assets based on in-house research and development.

Lilly Chairman and CEO David Ricks said during the company's first quarter earnings call on April 24 that "strategically, we understand we need to be active externally, and you can count on us to continue to look at all available

choices to add to our pipeline, in particular, in oncology." Ricks has noted that Lilly expects to source about one-third of its assets from outside the company going forward.

In oncology, Garraway said the strategy is built around the idea of targeting mechanisms that are known to be essential to the survival of cancers cells or to their ability to evade attack by the immune system.

"We spend a lot of time prioritizing our own internal efforts to make rooms for things like [pegilodecakin], but also coming up with a decision framework that draws from our understanding of the science and how we might develop it. Are there ways to enrich patents molecularly or characteristics that might make them more likely to respond?" he explained. "All of these go into how we recognize what assets, either internally or externally, might have potential. This happens to be an interesting IO candidate, but our strategy is not limited to IO in that regard."

Garraway said Lilly liked the preclinical data for pegilodecakin, which showed that pegylated IL-10 as a single agent clearly activated CD8-positive T-cells and caused tumor regression, which is how an IO agent should work. "We thought that the biological rationale was strong for that reason and we also liked the clinical data that we've seen [including] single-agent activity in some tumors in patients," he said.

## Using IL-10 To Boost Checkpoint Inhibitors

Lilly also was encouraged by initial results for pegilodecakin in combination with existing immune checkpoint inhibitors. "Overall, the package looked like it had the potential to bring additional value to patients across multiple types of cancer. There was no single thing that put it over the hump, but it was the aggregate picture that made us feel like this was a potentially interesting asset," Garraway noted.

The aggregate picture that the Lilly Oncology executive described is in line with what Armo President and CEO Peter Van Vlasselaer envisioned when he spoke with *Scrip* in 2016 about the company's $50m Series C venture capital round.

"The first wave of immuno-oncology has taken place and the first generation molecule is PD-1," Van Vlasselaer said at the time.

"The generally accepted viewpoint is that we can combine immuno-oncology agents and improve the outcome. The question will be, what are those molecules and what will be the next wave in the space?" he continued. "You have a cornerstone molecule for checkpoint inhibitors and molecules that target the microenvironment and others that prime tumors to be responsive. We think [the latter] will be the cytokines [like IL-10, 12 and 15]. They are potent immune stimulators."

# ABOUT THE SPONSORS

## About Heidelberg Pharma

Heidelberg Pharma AG is a biopharmaceutical company based in Ladenburg, Germany. Heidelberg Pharma is an oncology specialist and the first company to develop the toxin Amanitin into cancer therapies using its proprietary Antibody Targeted Amanitin Conjugate (ATAC) technology and to advance the biological mode of action of the toxin as a novel therapeutic principle. This proprietary technology platform is being applied to develop the Company's proprietary therapeutic ATACs, as well as in third-party collaborations, to create a variety of ATAC candidates. The proprietary lead candidate is HDP-101, a BCMA ATAC for multiple myeloma.

The Company has entered into partnerships to further develop and commercialize its clinical assets MESUPRON® and REDECTANE®, while RENCAREX® is available for out-licensing and further development. Heidelberg Pharma AG is listed on the Frankfurt Stock Exchange: ISIN DE000A11QVV0 / WKN A11QVV / Symbol WL6. More information is available at **www.heidelberg-pharma.com.**

## About iron4u

iron4u was founded in Denmark in 2012 by investors from 5 European countries – including Germany and Denmark.

iron4u's main focus, in cooperation with the German Company Serumwerk Bernburg, is to develop and register a patented human injectable iron product based on Polyglucoferron and to market the product world-wide.

The company focuses on improving the treatment of iron deficiency for humans. In addition, iron4u have marketed products aiming at optimizing treatment of iron deficiency in the veterinary setting.

More information is available at **http://iron4u.com**

## About Specialised Therapeutics

Specialised Therapeutics is an independent, international biopharmaceutical company providing specialist medicines and technologies to patients in Australia, New Zealand and across South East Asia.

Founded a decade ago with a single oncology product, the company has since built a diverse and robust portfolio of specialist medicines, successfully identifying and collaborating with international biotechnology and pharmaceutical partners and expertly commercializing their products in these niche markets.

ST's mission has always been to provide innovative medicines and technologies to patients where there is an unmet medical need. It's broad therapeutic portfolio currently includes novel agents in oncology, haematology, neurology, ophthalmology and supportive care.

Additional information can be found at **www.stbiopharma.com**

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