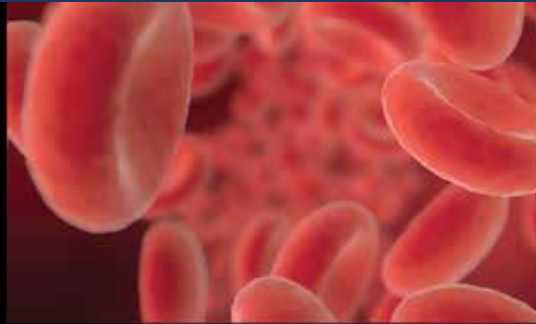
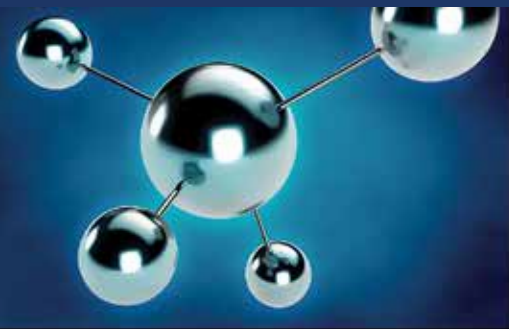


In Vivo

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JUNE 2019



HARD PROBLEMS IN HEALTH CARE



A 'Blood Pressure Test'
For Dementia

MIT's Robert Langer On The Converging
Science Of Drugs, Devices And Delivery

Is A Universal Flu Vaccine Still
A Lifetime Away?

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In Vivo

Informa Pharma Intelligence

June 2019



HARD PROBLEMS IN HEALTH CARE

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A 'Blood Pressure Test' For Dementia

ASHLEY YEO

The attention accorded to degenerative brain conditions has been slow to reach the levels given to the more visibly quantifiable conditions, such as cardiovascular disease and oncology. Playing its part to push back the boundaries is Cognitivity Neurosciences, a London-based company with an innovative tool that uses AI to test subjects for the early signs of dementia.

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Understanding An Evolving Medical Cannabis Market

ED SILVERMAN

In case you have not noticed, a new gold rush appears to be underway. Buoyed by surging interest in medical cannabis, big and small companies from around the world are racing to take advantage of the potential for the marijuana plant to cure numerous diseases and take its place in the pantheon of pharmaceutical products.

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Is A Universal Flu Vaccine Still A Lifetime Away?

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Influenza is a wily foe. It shows up each winter having taken a slightly different guise to outwit our existing immune defenses, but always keeps up its sleeve an ability to shape-shift to an entirely new form that could crash straight through them.

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New Science As A Growth Strategy: Three Dimensions To Guide The Transition From Old To New

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Finding innovative ways to adapt the biopharma business model to external and internal challenges is a key competitive differentiator for today's C-suite leadership.

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From The Editor



LUCIE ELLIS

world's first CAR-T therapy approved for multiple myeloma.

In a recent report, Biomedtracker highlighted various products that are anticipated to enter the US market in 2020 for the first time or in new indications. These therapies represent novel drug classes, large market opportunities and treatments that are predicted to heavily impact the current standard of care for certain indications. Included on the list are the likes of Intercept Pharmaceuticals' Ocaliva (obeticholic acid), which is in line to become the first approved treatment for NASH (non-alcoholic steatohepatitis), and Celgene and bluebird bio's chimeric antigen receptor (CAR) T-cell treatment idecabtagene viciuecel (bb2121), a product candidate that has the potential to be the

Overall, Biomedtracker believes that more than 50 candidate medicines, across 15 broad therapeutic categories and involving more than 60 companies, may reach their first markets over the next 12 to 18 months.

While these imminent success stories showcase novel innovation and highlight progress in the industry, there are still many tough questions plaguing medical research and the health care market. For June, *In Vivo* has focused on some of these harder problems in health care.

Our writers have focused on new markets and the challenges they present: such as the boom in medical cannabis research and development, and its potential as a treatment for various maladies.

In Vivo's team has also highlighted manufacturing issues that still need to be conquered to fully unleash the power of cell and gene technologies, and they have delved into the burden of influenza and the scientific challenges surrounding the development of a universal vaccine.

Finally, in the first article as part of a new feature series on pioneering laboratories in the life science sector, William Looney sat down with MIT's Robert Langer – arguably the most inventive and prolific life scientist of his generation – to identify key challenges in medicine. He discussed the budding entrepreneurial impulse in academia and emphasized the importance of investing in basic, foundational research.

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Up-Front

SNAPSHOTS FROM JUNE'S CONTENT

Fresh approaches to early testing for dementia are increasingly common, but the resulting technology has tended to fall short in terms of results. London-based Cognetivity Neurosciences has been developing a compelling solution, the Integrated Cognitive Assessment test.

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As a sign of growing interest in marijuana businesses more broadly, public and private cannabis firms raised more than \$13.5bn through 557 deals in 2018, up from \$2.7bn and 378 deals the year before.

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Advances in influenza virology, immunology and vaccinology make the development of a universal influenza vaccine more feasible than a decade ago.

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Deal-making between pharma and AI specialists is becoming increasingly commonplace, as the industry seeks external pioneers to validate the technology, in addition to building internal data science teams.

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“There have been continuous advances in our understanding of human biology since the turn of the century. Much remains to be revealed about biology and its application to medicine, but significant groundwork has been laid.”

– Robert Langer,
MIT
PAGE 30

■ Around The Industry

PharmAI – Industry Is Smartening Up To Potential Of Artificial Intelligence

Artificial Intelligence (AI) has enormous potential in changing the delivery of health care and improving patient outcomes, with applications in pattern detection, patient monitoring, disease diagnosis and treatment selection. The rationale is that AI can be used to enhance the decision-making process, taking into account far more data than are available to physicians via conventional means. The addition of machine learning (ML) algorithms enables the AI to become better over time, increasing the accuracy or timeliness of its recommendations. Recognizing this broad potential, the FDA has recently sought to spur the industry with its discussion paper on regulating Software as a Medical Device (SaMD) products.

The application of AI and ML techniques to the pharmaceutical industry will have less of a direct impact on patients, although it may be fundamental to improving R&D productivity and sustaining the current pace of innovation. Leading pharma companies are almost universally detailing such digitalization initiatives in their investor-facing materials, showing that they are at the forefront of this vital industry trend.

PHARMA COMPANIES ARE ACCELERATING ADOPTION OF AI-ML TECHNOLOGIES

Deal-making between pharma and AI specialists is becoming increasingly commonplace, as the industry seeks external pioneers to validate the technology, in addition to building internal data science teams. Over the past two years, Informa Pharma Intelligence's Strategic Transactions has noted 13 such alliances with specific mention of the AI or ML learning capabilities that one partner brings. Of these, 10 deals have occurred in the past 12 months, pointing toward an acceleration in the adoption of such technologies (see *Exhibit 1*).

Among these deals are notable big pharma examples such as Roche, Pfizer Inc., AstraZeneca PLC, GlaxoSmithKline PLC, Bristol-Myers Squibb and Sanofi. The alliance between bluebird bio and Gritstone has the highest potential deal value, with milestone payments of up to

\$1.2bn, in addition to \$20m up front. Exscientia has now concluded several major deals, each with different pharmaceutical companies, showing that these platforms are being applied to individual discovery programs and are not being used in exclusive arrangements with a single licensee. Furthermore, the approach is not restricted to any particular therapeutic area, with examples spanning oncology, immunology, central nervous system disorders, cardiovascular diseases and metabolic disorders. The extent of collaboration is so far focused toward early preclinical research, such as target identification and lead optimization. Still, the potential for AI-ML is certainly broader.

AI-ML AS MEANS TO IMPROVE R&D PRODUCTIVITY

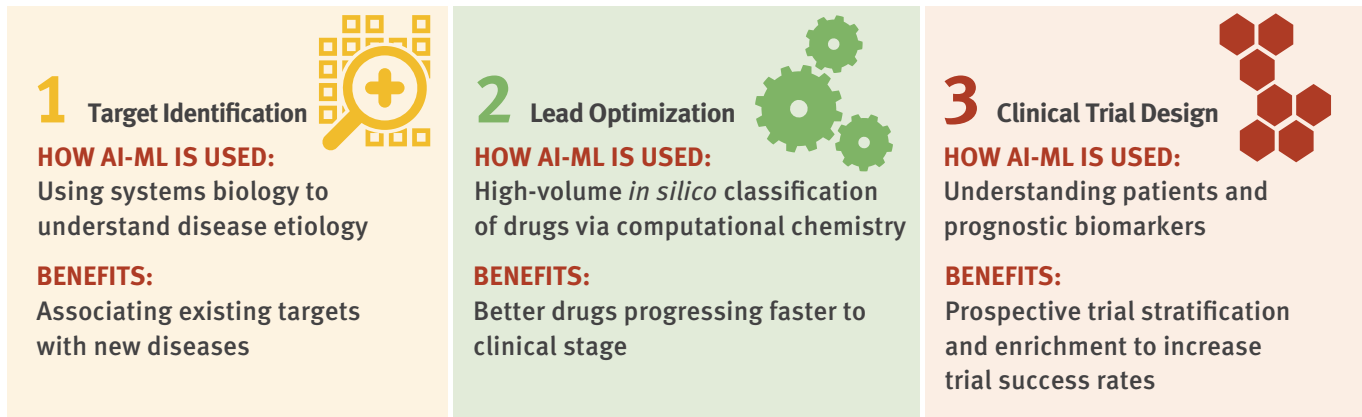
Many of the current deals between pharma and AI-ML experts have a specific R&D project in mind, aiming to bring better compounds into clinical development at a faster rate, thereby shortening development timelines and improving the eventual likelihood of approval. It may well be that better understanding of complex diseases will yield previously unknown drug targets – and potentially entirely new, differentiated breakthrough therapies. Nevertheless, the core business case behind pharma's adoption of AI-ML techniques is as a productivity initiative, allowing pharma to realize a higher return on its R&D investment.

With estimates for the cost to bring a new drug to market continuing to spiral upwards – the most recent calculation by Tufts Center for the Study of Drug Development places the figure at \$2.6bn – anything that can reverse this trend is sorely needed. As AstraZeneca R&D chief Mene Pangalos simplified in an interview with *In Vivo's* sister publication *Scrip*: “It takes many years to get a candidate into the clinic so could you write an algorithm that could speed that process up and do it more efficiently?”

While AI-ML does not replace basic research into human biology and disease etiology, its great strength is that it is able to make connections within complex data sources that no human brain could realistically hope to make, without any prejudice. The intuition of scientists can be augmented by the processing of unfathomable amounts of information to arrive at the best solutions based on the data available. This allows an unbiased approach to the question at hand, with any new data and insights generated further strengthening the underlying AI-ML platform. This is immediately useful for diseases that are currently poorly defined or understood, potentially discovering new targets whose relationship to the disease state is not obvious. BenevolentAI itself has created a drug discovery program for amyotrophic lateral sclerosis based on a target previously evaluated in breast cancer. AstraZeneca has pivoted the development of saracatinib away from hematological cancers and into idiopathic pulmonary fibrosis based on the insights of digital health and AI pioneer Joel Dudley at Mount Sinai in New York. The microbiome field is another rich resource for AI-derived insights, considering the innumerable interactions between human biology and the 10–100 trillion symbiotic micro-organisms within

Exhibit 1

AI-ML Inputs Into The Traditional R&D Process



each of us, increasingly being recognized as an organ in its own right, or even our second genome.

Even with a sound scientific basis for a drug discovery project, the design and selection of the best drug candidate is limited by the resources available. There is a trade-off between the time spent on lead optimization and the need to progress a candidate into the clinic, which inevitably contributes to the failure of drugs due to unforeseen pharmacokinetic, toxicity or efficacy shortcomings. Existing knowledge around drug-like properties and the target interaction can be distilled with AI into better drug candidates for preclinical testing. UK-based Exscientia claims to deliver clinical-stage drug candidates in one quarter of the time of traditional approaches, suggesting the reason for its popularity as a partner for pharmaceutical companies.

A drug's success can hinge solely on the design of its clinical trial program, which is another area in which AI can help to plot the best course. A more complete understanding of the disease state, target, drug and patient characteristics can enable prospective patient stratification for treatment responders. This increases the likelihood of a favorable outcome in the clinical trial, or avoids the scenario in which expensive Phase III trials are repeated after the best design is only uncovered due to retrospective analyses. Even if a drug reaches the market, razor-thin differences between competitors can be exaggerated by clinical trial design, yielding vastly different market

prospects. Taking the current crop of programmed death-1 (PD-1) inhibitors: it is commonly asserted among prescribers that the drugs within the class are extremely similar. The correct choice of patient group, biomarker, background therapy or comparator arm in a pivotal clinical trial may potentially be worth many billions of dollars over the lifetime of the drug. While the advent of AI-ML may have come too late for the likes of Opdivo (nivolumab; Bristol-Myers Squibb/Ono Pharmaceutical) and Keytruda's (pembrolizumab; Merck & Co.) initial development, it can absolutely shape the next wave of immuno-oncology, matching non-responding patients to the most appropriate drug regimen based on biomarker data and known mechanisms of PD-1 inhibitor resistance. Pfizer instigated a collaboration with IBM in December 2016 with this in mind.

RECONCILING THE HYPE OF AI-ML AND SHORTCOMINGS IN DRUG DISCOVERY

There is undoubtedly an element of "fear of missing out" driving the adoption of AI-ML that accompanies the uptick in deal-making lately. Early pioneers such as Exscientia and BenevolentAI are clearly striking the right chord with their technologies, marketing them as essential solutions for modern drug discovery. However, we are yet to achieve proof-of-concept for an AI-enabled drug discovery program to result in an approved, successful product. And even when this does occur, it will be difficult to quantify the

exact benefit that the AI approach added in terms of timelines, R&D spend and clinical benefit, unless a lesser-informed, competing pharma company opts to become the placebo. It will only be with many approved examples that it would be possible to validate claims of better drugs and higher likelihood of approvals, but arguably AI-ML will come up short in terms of fixing the true bottleneck of drug discovery: translating preclinical research into clinical proof-of-concept at Phase II. The AI can only be as smart as our basic understanding of human biology allows, so drug discovery is always going to be an iterative process, with failures being a necessary component. Perhaps tellingly, IBM is now stopping sales of its Watson AI in the field of drug discovery, with previous reports that its application in oncology clinical practice has not been able to live up to IBM's own lofty expectations.

Regardless of how much AI-ML is actually able to deliver, if these technologies can help to better understand diseases, create fully optimized drug candidates and test them in patients in the smartest way possible, it would be negligent for pharma executives not to make use of their capabilities. ❖

IV124275

DANIEL CHANCELLOR

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Science Matters: Glimmers Of Hope For Treating ALS

Much of the buzz at the annual meeting of the American Academy of Neurology (AAN) in early May was around competitive drugs for treating spinal muscular atrophy (SMA), including Biogen Inc.'s Spinraza (nusinersen). Biogen also presented late-breaking interim data from a Phase I/II clinical trial of its antisense amyotrophic lateral sclerosis (ALS) drug candidate tofersen (BIIBo67). Only 2% or so of the ALS patient population has a mutation in the superoxide dismutase 1 (SOD1) gene, the target of tofersen. But the tofersen data, coupled with the success of Spinraza, which is also an antisense oligonucleotide (ASO) aimed at a gene mutation affecting neurons, are encouraging signs that targeting genetic drivers of ALS with ASOs or other gene-altering drugs could halt progression of several forms of the disease.

The tofersen data, while preliminary, provided assurance that the drug hits its target and is consistent with the belief that it may slow disease progression. Ten people who were given 100 mg of the experimental drug had a 37% reduction of the SOD1 protein in cerebrospinal fluid (CSF) compared with 12 people who received a placebo. "The SOD1 data is exciting," said long-time SVP of research, C. Frank Bennett, of Ionis Pharmaceuticals Inc., which licensed tofersen to Biogen. "It shows that if we are on target, we can find a therapy."

Ionis began a clinical trial of a first-generation ASO to SOD1 back in 2010. The company subsequently developed better screening methods and oligo designs, and decided to put the original drug on hold, Bennett said. Biogen, which also licensed Spinraza from Ionis, optioned Ionis' SOD1 program, initiating the current trial with the later-generation molecule in 2015. Over the past six years, the parties have developed a broad strategic partnership around the use of ASOs to treat neurological diseases.

"One of the opportunities we gained from working with Biogen was it had conducted a very large Phase III program in ALS with another drug, dexamipexole," Bennett said – a study that ultimately failed to show a clinical benefit. But learnings about trial design and outcome measures enabled Biogen to both accelerate development of the ASO against SOD1 and to get outcome measures in a short-term study that would give a more robust indication the drug was working.

Although at least 150 different SOD1 mutations are known, each causative of ALS (and no other disease), about half of North American patients have the same one

– an alanine to valine substitution at codon 4. The typical survival for these patients, who have exclusively lower motor disease, is nine months with only a few outliers who live longer, to perhaps a year from onset.

"These patients deteriorate very quickly," Bennett said. "That allowed ascertainment in a short time that the drug looked like it was providing positive clinical signs."

Misfolding of SOD1 could also be contributing to some of the neuropathology in sporadic ALS (disease that cannot be traced to a familial cause), including axonal transport. Researchers have detected misfolded forms of SOD1 in CSF or tissue sections from autopsy samples. "It remains to be seen if removing SOD1 will benefit," Bennett said. "That's a clinical study that needs to be done."

The most frequent cause of ALS – both of inherited or sporadic disease – is a repeat expansion in the gene, *c9orf72*. "Using an antisense oligonucleotide to suppress the expression of the *c9orf72* gene or at least a piece of the gene is, we think, an effective therapeutic strategy," Don Cleveland, chair of the department of cellular and molecular medicine at the University of San Diego's Ludwig Institute for Cancer Research, said in an interview.

Cleveland, who invented Spinraza and worked with Ionis to bring its first SOD1 ASO into the clinic, has also worked with Ionis to show that an antisense to *c9orf72* can be delivered broadly to the nervous system. But unlike SOD1, which is strongly penetrant, for patients with the *c9orf72* mutation but no family history of ALS, expansion of the gene causes disease in only a portion of the people who inherit the mutation. "It is a causative gene but you are

not assured of getting the disease even if you have the expansion," Cleveland said. Biogen optioned rights to Ionis' *c9orf72* ASO and started a clinical trial of it (as BIIBo78) in September 2018.

"It's possible that the consequence of *c9orf72* expansion might be occurring in some of the sporadic ALS patients," added Roy Parker, biologist at the University of Colorado, Boulder.

The disease process in patients with the *c9orf72* expansion might occur through RAN (repeat-associated non-ATG) translation. Repeat expansion mutations in *c9orf72* can produce RAN proteins, which accumulate in disease-relevant tissues with downstream consequences. Understanding how RAN translation occurs, the cellular factors that contribute to RAN protein accumulation, and how these proteins contribute to disease should lead to a better understanding of the basic mechanisms of gene expression at work in a variety of diseases, including ALS and also frontotemporal dementia (FTD). Ionis focused on ALS because the conduct of the study and the clinical outcome measures are better defined than in FTD. "The plan would be to study the drug in FTD once we have more clinical data in ALS," Bennett said.

REACHING A BROADER POPULATION

Targeting the downstream effects of mutations in the TDP-43 gene is encouraging another gene-targeting strategy in ALS – one that, unlike SOD1 or even *c9orf72*, could be used in a broader ALS patient population. Genetic variation in TDP-43 causes that protein to mislocalize – a phenotype observed in the majority of ALS patients. This mislocalization presumably causes a loss of function of TDP-43, leading to efforts to enhance the function of TDP-43 as a strategy for treating sporadic ALS.

A paper in *Nature* November 22, 2018, showed that TDP-43 has a significant cytoplasmic role during muscle development or generation. "We think that's shared in neurons," Parker, the paper's senior author, told *In Vivo*. While silencing TDP-43 itself is problematic given its important

cellular functions, the paper suggests an alternative therapeutic strategy for ALS that involves targeting ataxin-2, which when decreased in model systems suppresses TDP-43 toxicity. Moreover, intermediate-length polyglutamine expansions in the ataxin-2 gene increase risk of ALS.

Ataxin-2 is another potential target for an ALS ASO; it has been implicated both in spinal cerebellar ataxia 2 (SCA2) and also ALS. According to Bennett, if an individual has a long polyglutamine repeat, it could lead to SCA. But those with intermediate repeats are at high risk for developing ALS. An antisense targeting ataxin-2 “might be of benefit for treating all patients with ALS,” he said.

Importantly, the Parker group identified the presence of TDP-43 “myo-granules,” which like amyloid-like aggregates, could affect neurological function. In an accompanying *News & Views* in the same issue, Lindsay Becker and Aaron Gitler of the Stanford University School of Medicine said the paper “sets the stage for future work” characterizing the physiological function and regulation of TDP-43 myo-granules, and for investigating how these complexes might contribute to disease. (Becker and Gitler, for their part, have been exploring the use of ataxin-2 knock-downs as potential therapy.)

Another recent study, by Cleveland and collaborators from Kevin Eggan’s group at Harvard University, demonstrated that whenever the function of TDP-43 is lost, which is observed to be the case broadly in sporadic ALS, there is suppression of expression of the gene *Stathmin2* (*STMN2*), which is involved in axonal regeneration.

“When you lose TDP-43, the original RNA transcript – the pre-RNA of *STMN2* – is aberrantly spliced and prematurely polyadenylated, making a useless RNA that does not encode the functional protein,” Cleveland said. So a partial loss of TDP-43 will lead to a larger loss of *STMN2*. That, in turn, will lead to suppression of the ability of motor neurons to regenerate after an initial injury. The authors propose to use the antisense oligonucleotide approach, modeled after the Spinraza approach, to restore the correct RNA maturation of the *STMN2* RNA.

In addition to the ASO approach, it may be possible to use a viral vector such as AAV to introduce a gene encoding a short hairpin RNA to suppress *SOD1*. AveXis Inc.,

which was acquired by Novartis AG in 2018, is contemplating such a trial.

CLINICAL DEVELOPMENTS COMING THROUGH

Since the end of Biogen’s dexamipexole program, only Cytokinetix Inc., with partner Astellas Pharma Inc., has conducted a relatively large-scale ALS study. A failed Phase III VITALITY-ALS trial of its fast skeletal troponin activator, tirasemtiv, completed in 2017, and the company presented Phase II data at the recent AAN meeting on a successor compound, reldesemtiv. Although the trial did not meet the primary endpoint, “we are encouraged by the results of the trial as they further validate the potential of skeletal muscle activation in treating patients battling ALS,” said Fady Malik, Cytokinetix’ EVP of research and development. “We believe the results support progression of reldesemtiv in further clinical trials toward potential registration.” Reldesemtiv is intended to slow the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers.

In ALS, the neurons that are dying are primarily motor neurons, either upper or lower motor neurons. Those neurons enervate (weaken) muscle. Improving muscle function and increasing muscle strength might have a positive feedback on the neuron so it is not working as hard, and could perhaps prolong survival of the motor neuron. Removing some of the toxic stress that in ALS is probably contributing to the death of motor neurons, and dampening down that excitatory pathway, could also preserve motor neurons.

That said, “it seems the pathology of ALS is dependent on neuronal death,” Parker said. So while treating muscle-related aspects of the disease could mitigate some phenotypes transiently, it likely will not affect progression substantially.

Nonetheless, most of the upcoming high-impact ALS clinical study events are around compounds that aim to ameliorate symptoms. Only Brainstorm Cell Therapeutics Inc.’s NurOwn (autologous mesenchymal stem cells engineered to produce neurotrophic factor) can be seen as potentially disease-modifying.

Other notable trials include a Phase II study from Amylyx Pharmaceuticals Inc. of AMX0035, a combination of sodium phen-

ylbutyrate and tauroursodeoxycholic acid, which work together to maximize cellular mechanisms linked to cell death in ALS; and Finnish Orion Corp.’s Phase III study with levosimendan which, like Sanofi’s Rilutek (riluzole), the first FDA-approved ALS drug, in 1995, treats respiratory symptoms. Levosimendan was previously approved as a treatment for acute heart failure and Orion thinks it may be applicable to ALS. Candidates recently entering clinical trials include IPL344 from Immunity Pharma Ltd., which activates the PI3K-Akt signaling pathway in a variety of cells, including neurons, inducing pro-survival and anti-inflammatory processes; and DNL747, an RIPK inhibitor from a collaboration between Sanofi and Denali Therapeutics Inc.

“Despite having advancements with respect to *SOD1* and *c9orf* and other genes, together those only aggregate to contribute to about 10% of ALS cases,” said Cytokinetix’ president and CEO Robert Blum. “The other 90% are still sporadic, for which we don’t understand the pathogenesis of the disease. So, if you can slow disease function, and that includes extended function and extended survival, regardless of cause, that should be deemed disease modifying.”

For the most part, ALS is not a disease where there is a relatively straight line from a gene target upregulated by antisense or gene therapy, Blum said, where one can assume the therapy hypothesis will support the drug development in a more focused way. “ALS presents in so many different ways: upper motor neuron and lower motor neuron, familial and sporadic,” he said. “From our standpoint, regardless of what causes the disease, patients all tend to suffer through the same kind of functional impairments that we think a muscle directed approach should address,” he noted. “That’s where we believe that reldesemtiv, alongside of gene-directed therapies, should be quite impactful and complimentary.”

IV124274

MARK RATNER

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HARD PROBLEMS IN HEALTH CARE

6 Of The Greatest Therapeutic R&D Challenges

1 DRUG RESISTANCE IN CANCER



- Growing evidence supports the importance of the tumor micro-environment in drug resistance as the main reason for the relapse and incurability of various cancers

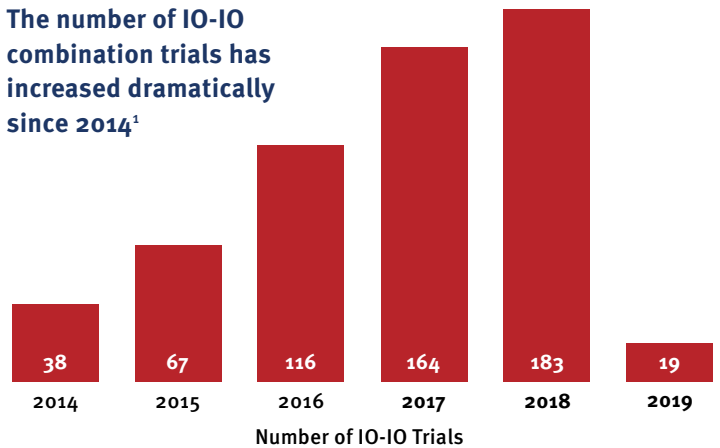
- Combination therapy is the leading approach to tackle resistance



56%

of all active immuno-oncology clinical trials in 2018 were combination studies

The number of IO-IO combination trials has increased dramatically since 2014¹



2 ANTIMICROBIAL RESISTANCE



- Antibiotic resistance is rising to dangerously high levels in all parts of the world
- Approximately 1.7 million patients in the US get an infection in the hospital each year; about 99,000 of whom die as a result

70%

of the bacteria causing such infections are resistant to at least 1 drug commonly used to treat these infections

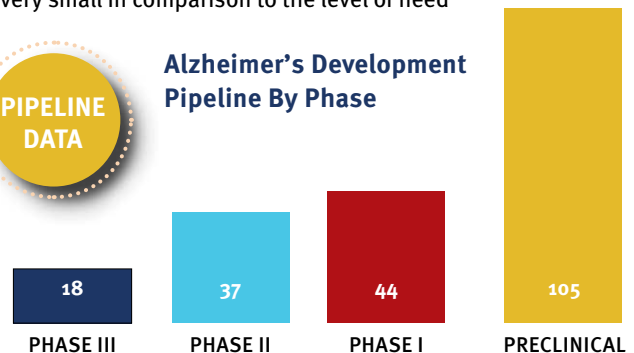
3 UNDERSTANDING DEMENTIA AND ALZHEIMER'S DISEASE



- There is no cure for Alzheimer's disease
- Dementia affects more than 50 million people worldwide
- This is expected to rise to approximately 152 million by 2050
- The sales value of Alzheimer's treatments is expected to reach \$5.5bn by 2024 for US, Japan and five major EU markets – still very small in comparison to the level of need



Alzheimer's Development Pipeline By Phase



¹Data correct as of April 2019 | Design: Gayle Rembold Furbert and Jean Marie Smith

4 REVERSING DAMAGE TO THE HEART



- Current treatments for heart failure focus on managing symptoms (like reducing blood pressure) but do not address the root problem
- Novel stem cell therapies have the potential to treat end-stage congestive heart failure due to their ability to reduce scar formation and prevent harmful inflammatory responses within damaged tissues
- Researchers are experimenting with a variety of stem cell therapies to transplant new cells, use tissue engineering to improve the survival or function of transplanted cells, and stimulate existing cells to generate new cardiomyocytes

PIPELINE
DATA

43 assets
in development for CHF (Phase I-Phase III)

10+ companies
are trialling stem cell approaches
to treating CHF

5 IMPROVED AND ACCESSIBLE DIAGNOSTIC DEVICES FOR RARE AND GENETIC DISORDERS



About 350 million people globally are affected by rare diseases

- The length of time from symptom onset to an accurate diagnosis is around 4.8 years for a rare disease
- Patients see an average of 7.3 physicians before a diagnosis is made
- More than 50% of rare diseases affect children; 30% of patients die before the age of 5

80%
of the 7,000 known rare diseases are genetic

6 LIMITATIONS OF ANIMAL MODELS



- From basic biology to translational medicine and clinical trials, animal models are an invaluable tool for inferring human biological responses
- Replacing animals with algorithms: researchers are developing computational models that crunch huge quantities of research data to predict the effects of certain products on an organism

Issues In Animal Models Versus Human Trials

- Animals used in studies are young and otherwise healthy, whereas in certain diseases patients can be elderly with many co-morbidities
- Assessment of the effect of a treatment in a homogeneous group of animals versus a heterogeneous group of patients
- Models used for inducing a disease or injury have insufficient similarity to the human condition
- The use of doses that are toxic or not tolerated by patients
- Differences in outcome measures and the timing of outcome assessment between animal studies and clinical trials

Sources: Alzheimer's Association, Biomedtracker, Datamonitor Healthcare, In Vivo, Strategic Transactions, UN Health Statistics, WHO

A ‘Blood Pressure Test’ For Dementia



The attention accorded to degenerative brain conditions has been slow to reach the levels given to the more visibly-quantifiable conditions, such as cardiovascular disease and oncology. Playing its part to push back the boundaries is Cognetivity Neurosciences, a London-based company with an innovative tool that uses AI to test subjects for the early signs of dementia.

BY ASHLEY YEO

A rapid visualization tool is being developed by Cognetivity Neurosciences that is expected to add options for the testing of pre-symptomatic cognitive impairment subjects.

The noninvasive test is claimed by the company to be unique from a design point of view, and it has applications in the non-clinical setting. There are also possible partnerships with pharma companies in the clinical trials space.

So what? With no effective therapies available to slow the progression of Alzheimer's, there is growing realization that the industry needs to do things differently. This company's answer is to use a sensitive visual categorization platform in conjunction with advanced AI algorithms to develop what it hopes might be seen as a “blood pressure test equivalent” for dementia patients.

Fresh approaches to early testing for dementia are increasingly common, but the resulting technology has tended to fall short in terms of results. London-based Cognetivity Neurosciences Ltd. has been developing a compelling solution, the ICA (Integrated Cognitive Assessment) test using natural images that are presented quickly to participants who are asked to accurately indicate whether they have seen a pre-specified image category. The test can be performed on an *iPAD*, potentially in any setting. The viewed images are processed in the visual cortex, a brain region associated with the earliest signs of neurodegeneration in conditions such as Alzheimer's disease (AD), and are translated to movement in the motor cortex, allowing evaluations to be made based on comparisons with an accurate dataset of clinically-diagnosed subjects. It is a technology that the company believes has applications in and beyond the clinical setting.

The involvement of Cognetivity, a Cambridge spin-out, in the technology began when one of its founders, Dr Seyed-Mahdi Khaligh-Razavi, a computational neuroscientist, was doing a PhD at Cambridge. The central aim of his research was to understand – and quantify – how much better the human brain is than computers at analyzing images. He noticed that there was an age-related fall-off over time in subjects' speed and accuracy in reacting to stimuli. Older people were less able to analyze – as expected. But that's where the idea for the CGN_ICA technology came from.

Dr Sina Habibi, co-founder and CEO of Cognetivity, decided with Khaligh-Razavi to look further into whether this was something worth investigating in from a dementia diagnosis point of view. The decision was taken then to write a code and develop proof-of-concept data for this visual challenge method, whereby images are represented on the retina and, transferred to the visual and pre-frontal cortex, with responses made using the motor cortex.

The rationale was explained by Cognetivity's COO, Thomas Sawyer, who said, “We have constantly been improving data capture and processing computational capabil-

ity, but not everything can yet be more efficiently done by computer.” Speaking to *In Vivo* about the opportunity ahead, he described how the company had developed a test that seeks to quantify the mathematical elements that affect human cognitive function. “By fine-tuning the elements of the test, they were able to come up with something that was very useable and repeatable,” said Sawyer, a University of Cambridge MBA. Sawyer joined the team five years ago, after meeting Habibi when Sawyer was mentoring at the business school in Cambridge. Khaligh-Razavi has MIT experience too, and was described by Sawyer as an “excellent academic,” capable of building proof-of-concept software platforms.

Clinical Applications

The technology has entered the phase of heavy validation, ahead of regulatory approval and scaling the platform. The validation trial for regulatory approval is being conducted at the Maudsley Hospital, London, and the study is designed to work for both CE marking (under the current EU Directives) and FDA and other regulatory jurisdictions thereafter. “We’re in the throes of carrying out the study, bearing in mind that the recruitment of subjects is one of the major challenges with this kind of trial.”

The images presented to the subject are very tightly controlled. “We work out at what point the subjects stop beginning to discern. In simple terms, it could be a full screen shot of a horse, or a more challenging forest or in-flight scene, featuring a small animal within the frame. That’s where the lack of learning effect comes in – if the subject can’t discern the animal in a particular image, they do not get better at doing this, the animal remains invisible.” Other tests can be learned over time, and this decreases their value as an objective measure. The ICA is a single task that engages a large proportion of the brain that no other test has used to date. It then uses sophisticated AI to analyze a multitude of data points in order to determine the likelihood of impairment.

“We deliver a wide range of images and can determine at what point the subject is unable to determine the animal.” Nobody gets all the images, said Sawyer. “We’re looking at the relationship between



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That’s where the lack of learning effect comes in – if the subject can’t discern the animal in a particular image, they do not get better at doing this test.

– Thomas Sawyer
Cognetivity

”

speed and accuracy for the different composition of the images,” he added. The images are broken up by white noise pictures, but the exposure to the images is very short: just 100 milliseconds for the visual cortex to make some sense of what is being presented.

The fundamental design of the test has no particular data component. “We’ve not seen anyone else going about this problem with this design point of view. It lends itself very well to the ability to pick up small changes,” he said. It is, by necessity, a very challenging task for the brain, but this means being able to test for the earliest stages of cognitive decline.

The AI side of it comes over and above that. “We’re able to use results from groups of subjects that we have controlled and in whom we know the clinical circumstances, and use these to train our AI. We’ve experimentally examined populations of MCI and mild AD patients – measuring their particular patterns of response to the varied stimuli – as well as a group with MS.”

Then, the company trains the algorithms behind the test to be predictive for each of these conditions. The algorithms can be updated. “That’s where the data science comes in and that really the growth area.” By conducting more and more well-controlled studies, Sawyer said, Cognetivity would be able to say more about the characteristics of the population being studied by the way that the subjects respond.

Bringing the test to market readiness for clinical use is very much tied up with the regulatory process. “We have fully-functioning, cloud-based software, with several architectures that work: that’s what we’re testing and validating.” Sawyer is confident of successfully crossing these bridges with what is essentially a non-invasive medical device.

Non-Clinical Applications

Professionals will use the clinical product as an aid to diagnosis/or for diagnosis, but the company is also developing non-clinical applications. The platform delivers a very objective measure of cognitive function. It tests how quickly and accurately the brain can react to difficult stimuli. It is a test that could find use in the airline or other industries,

THE ICA TEST

Cognetivity's ICA tool is a rapid visual characterization task, in which subjects are presented with a fairly short-duration of stimulus – a photo – and the subject is asked to determine whether or not they saw an animal in the image. It focuses on cognitive functions such as speed and accuracy of processing visual information which have been shown to engage a large volume of cortex, while being a predictor of people's cognitive performance. Monitoring the performance and functionality of these areas can be a reliable early indicator of the onset of disease.

The reason for animals as the target visualization theme is that the human brain detects animacy as a by-product of evolutionary development. A whole chunk of the brain is specifically involved in that, the bottom line being that humans are good at spotting animals, even in harder images, such as animals foraging or in flight in visually-complicated environments. At the very broad level, it's a neuroscience test that picks up very subtle changes in cognitive performance.

for instance to check the state of pilots' health and take-off readiness. Sawyer sees the potential of the technology as a personal health monitor. The company has already signed a commercial deal, a few months ago, with a provider of health monitoring software, dacadoo, to provide cognitive monitoring.

The ICA will be used in this case as part of a suite of health monitoring applications, providing vital information on users' cognitive health, where the primary customers are health insurance companies. They would get access to the platform for their clients, who, in return, would pay a lower premium. The personal applications extend to a person proactively self-monitoring their own health. This would involve the subject looking to baseline themselves over a period of time, learning

normal ranges and checking themselves against that. And against how well they are performing for their age range.

The databank being accumulated includes sleep patterns and heart rate. "You're able to chart yourself – it fits in with the whole trend of personalized medicine, allowing you to track your own progress and work out what is best for the individual, rather than being only able to compare to very crude population measures." Sawyer said the technology's ability to be used frequently and at home would allow much higher resolution monitoring than had been traditionally achieved using comparator technology.

The potential is great. Sawyer pointed to the biggest market, the US, where there are over 200 million visits to a primary health care practitioner every year. In Cognetivity's eyes, a large proportion of these are potential testing opportunities. Medicare has an insurance reimbursement code for cognitive assessment, at \$48 per test, which gives an idea of the size of the clinical market segment that can be addressed.

Conveniently for users, the test can be delivered through existing hardware and a cloud-based system. "There is potential for significant revenue. It's an enormous market based in the idea that we can alert people early to deterioration of cognitive function-related dementia." The company suggested that people should start testing around the age of 50-55, given that the outcomes are so much better if a diagnosis occurs at an earlier stage. "Our thought is that this market would take a lot of our focus," said Sawyer.

The Consumer Offering

Although the personal and consumer potential of the screen-based test, with its user-friendly touch-left/touch-right method of use, is very large, Cognetivity has been reluctant to be branded a B2C company. There is the sense that many have jumped on the Apps bandwagon, and Cognetivity wanted to ensure it is not seen as part of that trend, given that it is "a very serious science company" that has developed "a very serious clinical tool." Sawyer noted, "Until the point where we are well established as a professional and highly validated platform, we believe we should hold off from going

A PREDICTOR OF NEURONAL DAMAGE USING SOFTWARE ONLY?

Recent research data from ongoing studies involving the ICA technology shows a strong negative correlation between levels of blood plasma neurofilament light (NfL) and the ICA score, with the ICA score decreasing as NfL levels increase. This highly-significant correlation of 0.79 "clearly demonstrates" the ICA's ability to predict the presence of neuronal damage using software only. This correlation gives further validation of the ICA test as a reliable, yet non-invasive, measure of cognitive impairment caused by damage to nerve cells. Blood plasma biomarkers, such as NfL, have potential to be effective as a diagnostic procedure for clinicians, but these procedures are invasive and highly time-consuming.

into the consumer market."

Patient dementia groups see a huge gap in the treatment pathway. Sawyer said, "We have always described our technology primarily as a clinical tool, and associations like Alzheimer's Research UK say there is a definite dearth of practical, useable tools capable of early detection." The benefit of this clinical tool is that testing 15-20 years earlier than currently happens today leads to early results and provides the information that allows for behavioral adjustments. Two types of patient generally present: the worried well, in whom there is usually nothing very much wrong; and the late diagnosis subjects, who are already heavily impaired. "You would like to be seeing pre-symptomatic dementia sufferers, so you can make the necessary behavioral and social adjustments."

"This is expensive to do at a later stage." But also, a longer functional period allows people to prepare for what is before them. A recent study by the Alzheimer's Association calculated that if all people with dementia in the US were diagnosed early, the saving for the health

care system would be \$7.9tn over the cost of their lifetimes – so there are strong economic as well as social arguments for earlier diagnosis.

Studies into attitudes towards the onset of dementia in the US and UK show broadly that the majority of people would like to know early. And if disease-modifying therapeutics are also brought into the argument, better brain function retention will be the overall result. While none of the therapeutics currently in Phase II and III are proposing to regrow dead brain cells, if they are already helping to deal with amyloid build up to stop the advance of the brain impairment, early diagnosis will become even more important when effective therapeutics do become available.

Cognetivity is currently doing a small funding round to finance work on developing the opportunities, including on the non-clinical side, and would raise capital for scale-up costs after US FDA approval, which is expected any time after the beginning of 2020.

Developing a new platform for clinical practice is an ongoing process, and brings in the need to work with different stakeholders over time. So far, the work has mostly been jointly undertaken with the scientific community. Building up the body of science is a priority, as is growing awareness in terms of the clinical community. The NHS in the UK, for example, is famously difficult to engage with, necessitating a lot of careful preparation work. But the Cognetivity is building up momentum in that area. “Clinicians like it,” said Sawyer of the ICA test.

The BP Test Equivalent For The Brain

But the type of application that the NHS really needs is something more akin to a blood pressure (BP) test, noted Sawyer. The idea is that clinicians can check that things are OK, or verify whether it needs further examination, and/or whether to get on a treatment pathway very early. “There is a crying need for this type of application,” Sawyer said. “We’re just at the early stages, but an equivalent of a blood pressure test, in that it is a simple, cost effective and meaningful measure for the mental health arena is the impression we want to give.”

A RISING INCIDENCE WITH HIDDEN COSTS

Providing sustainable care across the continuum from diagnosis to the end of life requires timely diagnosis before treatment and care come into the equation. The WHO’s Global Action Plan on the public health response to dementia 2017-2025 also notes that people with dementia are less likely to be diagnosed for comorbid health conditions, which, when left untreated, can cause faster decline. In 2015, dementia affected 47 million people worldwide (or roughly 5% of the world’s elderly population), a figure that is predicted to increase to 75 million in 2030 and 132 million by 2050. Recent reviews estimate that, globally, nearly 9.9 million people develop dementia each year.

Cognetivity has also realized the need to factor in the bandwidth of clinicians to take on new or extra tasks. Senior NHS people, for instance, tend to be more open to trying something new if it does not disrupt what they already do. “We are working on some validation studies within the health care system so people can see what it does, and how simple it is,” Sawyer said.

If it appears to be just another extensive and time-consuming task that will place even more pressure on already stretched clinicians then it will be unlikely to be adopted. “If that’s the case, then it won’t happen: many systems and projects have fallen by the wayside for not being compatible with clinicians’ current working practices, so it is important to make sure that any solution fits in with clinical practice.”

The NHS England Long Term Plan and the revamped Accelerated Access Collaborative (AAC), with its promise of championing early diagnosis, seem to be two innovation-promoting vehicles that are coming out at in the UK just the right time for Cognetivity and its outcomes-based, non-invasive, value-based health-care

tool. “There seems to be quite a shift in awareness of the need to be able to bring innovative solutions into the NHS.”

Clinical Trials Opportunities

The pharma clinical trials advantages of using a technology like Cognetivity’s is a further promising avenue. It is set against the premise that companies are sinking billions of dollars into trials that are failing, and probably for a number of reasons. But Sawyer said it seemed obvious that if you’re looking for subtle system signals from a cognitive standpoint, and the trial is using older tools, that these signals might not be detectable, with a resulting impact on the potential for a successful outcome for these extremely expensive trials, and a corresponding effect on the value of the company.

The pharma industry needs a tool that is sensitive enough in trials to pick up some kind of signal. “There is potential for our platform in that area. In terms of social impact, it could be very profound in helping find signals that are hard to pick up. It’s what we are trying to do,” he said. It would appeal to slow-moving, risk-averse clients as a secondary endpoint. “There is a crying need for a tool that can be used to reliably measure and monitor small changes repeatedly.”

Cheaper, More Efficient, And Ready For A Pharma Link

The precise business model adopted by Cognetivity with regards to clinical trials remains to be seen. But it is able to integrate with other platforms, plug into data platforms, and manage data. “There is likely to be a quite obvious link between a large pharma company and what we do,” said Sawyer. Indeed, a partnership with a large pharma company on a non-exclusive basis is an important aim for the company. He added, “If you could pick up a signal in a clinical trial, you would also be able to detect it in a potential patient once the drug has been approved for the treatment.” Recruiting early-stage patients for trials is notoriously difficult. “There needs to be a much cheaper and more efficient way of doing it, and we feel our ICA can definitely help with that.”

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Comments:

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Understanding An Evolving Medical Cannabis Market



In case you have not noticed, a new gold rush appears to be under way. Buoyed by surging interest in medical cannabis, big and small companies from around the world are racing to take advantage of the potential for the marijuana plant to cure numerous diseases and take its place in the pantheon of pharmaceutical products.

BY ED SILVERMAN

“There’s no other way to describe this – medical cannabis is going viral,” says Giadha Aguirre de Carcer, CEO at New Frontier.

As medical cannabis gains more attention from patients and doctors to lawmakers and investors, market research firms have raced to issue bold projections. Global sales numbers range from large to larger, although such estimates should be taken with the proverbial grain of salt.

For now, big drug makers are largely expected to sit on the sidelines – but as more regulatory questions are settled, the market should start to look more enticing.

Consider Affinity Bio Partners. The privately held clinical research organization located outside Philadelphia, PA, is expanding its conventional business in the US to run a few tests overseas and is also starting to pull in more foreign clients. The number of medical cannabis trials will double this year, according to CEO Christina DiArcangelo Puller. “Things are on the upswing,” she said.

Then there’s Masaya Medical, another small company that is running pharmacokinetic studies and other tests on an oil derived from cannabis. The goal, said AnnaBelle Manalo, who has a PhD in cell and developmental biology from Vanderbilt University, is to understand its effect on the metabolic process and eventually gauge any interactions that may occur with prescription drugs, among other things.

At the other end of the spectrum, Sandoz – the big generic drug maker that is owned by Novartis AG – has also joined the fray. The company is in the early stages of a wide-ranging deal to market and eventually develop medical cannabis products with Tilray, which is one of the fastest-growing and highest-profile purveyors of medical marijuana in Canada.

There are countless examples across the globe as hopes rise that medical cannabis will increasingly pass muster with regulators and payers, and become a commonly prescribed item found in household medicine chests, physician offices and maybe even hospitals to treat a wide variety of maladies. “There’s no other way to describe this – medical cannabis is going viral,” said Giadha Aguirre de Carcer, CEO at New Frontier Data, a market research firm that specializes in studying the medical marijuana market. She estimates there are 1.2 billion people worldwide who are suffering from medical conditions for which medical cannabis has shown therapeutic value.

Exhibit 1

10 North American Public Cannabis Companies Active In Medical Market

COMPANY	LOCATION	TRADED	FOUNDED
Aurora Cannabis Inc.	Canada	Toronto Stock Exchange	2013
Canopy Growth Corporation	Canada	New York Stock Exchange	2013
Namaste Technologies Inc.	Canada	Toronto Stock Exchange	2005
Cronos Group Inc.	Canada	Toronto Stock Exchange	2012
Aphria Inc.	Canada	Toronto and New York Stock Exchanges	2014
HEXO Corp.	Canada	New York Stock Exchange	2013
The Green Organic Dutchman Holdings	Canada	Toronto Stock Exchange	2012
Tilray Inc.	Canada	NASDAQ	2013
CV Sciences Inc.	US	NASDAQ	2010
CannTrust Holdings Inc.	Canada	New York Stock Exchange	2015

SOURCES: In Vivo; The Marijuana Index

Indeed, the potential seems unbridled. As medical cannabis gains more attention from patients and doctors to lawmakers and investors, market research firms have raced to issue bold projections. Global sales numbers range from large to larger, although such estimates should be taken with the proverbial grain of salt, since the data often encompass products containing cannabis that may not have been tested for treating a medical condition.

Even so, analysts suggest that changing mindsets are signaling wider acceptance for a notion that traditionally generated social stigma. The list includes everything from gastrointestinal and central nervous system disorders to rare genetic diseases and different forms of cancer that, sooner than later, may be treated with a licensed pharmaceutical that is based on cannabinoids, or the chemicals found in marijuana.

Already, unregulated medical cannabis may be gaining traction at the expense of prescription drugs. A recent study found that 78% of 450 adults attending a forum in the US on cannabis law reform reported using a cannabinoid to help treat a medical or health condition. Given the setting, the respondents may have been predisposed to such behavior. But significantly, 42% had stopped taking a pharmaceutical and 38% used less of a prescription medicine as a result, accord-

ing to the study published by University of Michigan researchers in the *Journal of Psychoactive Drugs*.

Addressing The Opioid Crisis

“And don’t forget,” noted Aguirre de Carcer, “there could be a massive impact on the opioid crisis,” which is a vexing policy issue in the US. She maintains that a medically validated alternative to addictive painkillers could win over lawmakers and readily transform the way that pain is treated. And in doing so, this could readily expand, and possibly cement, commercial use for such a salve.

Indeed, a study published last year in *JAMA Internal Medicine* found that medical marijuana laws were associated with lower opioid prescribing rates for Medicaid enrollees. Another study published in the same journal found that Medicare Part D prescriptions filled for all opioids decreased by 2.1 million daily doses per year when a state instituted any medical cannabis law, and prescriptions for all opioids decreased by 3.74 million daily doses per year when medical cannabis dispensaries opened. Yet another *JAMA Internal Medicine* study in 2014 even suggested there were fewer opioid deaths in states where marijuana was legalized, although a study published earlier this month in *PNAS* questioned these findings.

Of course, these studies represent snapshots and the medical marijuana involved was not approved by a regulator. Just the same, the findings underscore that attitudes are shifting, according to George Pappas, CEO of Schedule 1 Therapeutics, which is in running preclinical tests for using medical cannabis to treat neurological and central nervous system disorders. “We’re on the verge of a new frontier in medicines made from a plant that’s still illegal and the butt of a joke. Meanwhile, communities across the country are seeing devastation from opioid prescribing patterns that had gone ignored until recently,” he said. “If I try to connect the dots, society is making efforts to course-correct.”

This all adds up to an ever-growing number of companies that are seeking to develop and test potential prescription products that are derived from cannabis, although data is hard to come by, largely because this remains a nascent space that is overshadowed by the so-called recreational, or adult-use, market. But as a sign of growing interest in marijuana businesses more broadly, public and private cannabis firms raised more than \$13.5bn in 557 deals in 2018, up from \$2.7bn and 378 deals the year before, according to Virdian Capital Advisors, an investment banking firm that specializes in the cannabis sector.

When it comes to the regulated phar-

unsettled. Consider some of Europe's biggest markets. Two years ago, Germany legalized medical marijuana, prompting approximately 142,000 prescriptions to be written in 2018, according to the German Cannabis Association. However, insurance and physician education remains spotty.

In the UK, the National Health Service in England last year classified all but one cannabis-based medical product as unlicensed, and the agency has also restricted prescribing to physicians listed on a special register due to limited clinical evidence.

In France, the National Agency for Medicines and Health Products Safety, or ANSM, late last year recommended that medical cannabis should be available for several conditions – chronic pain, severe forms of epilepsy, as part of oncological care, palliative care, and multiple sclerosis. A more complete review, though, is under way and the government must still determine how to make products available.

The biggest question marks, however, are hovering over the US, where the FDA is still grappling with the best way to regulate medical cannabis. Unfortunately, the country has a hodge-podge approach to regulation and legality.

Although 33 states have declared that medical cannabis is legal, this can be deceiving because this status extends to products that are not approved by the FDA. Accelerating legalization has sanctioned use of oils and creams that typically contain two different compounds found in the marijuana plant – THC, or tetrahydrocannabinol, which has psychoactive properties and CBD, also known as cannabidiol. For instance, Epidiolex, the GW Pharmaceuticals medicine, is a formulation of highly purified cannabidiol.

This is where oversight gets tricky, though.

CBD may generally be legal on a federal level, as long as a product containing is not intended to be used for a medicinal purpose. Meanwhile, a growing number of CBD-based products make medical claims, often resembling the types of claims that a prescription drug would boast. The FDA has jurisdiction over cannabis compounds and would expect any product making such claims to first

conduct rigorous testing, but is still sorting out oversight. For now, though, CBD products are appearing online and on counters at pharmacies, retailers and even gas stations, blurring the lines in the same way as some dietary supplements do with prescription medicines.

A Complex US Environment

Another issue is at hand. In states where medical marijuana is legal, anyone given a prescription can obtain such a product at a dispensary, instead of the conventional route from a licensed pharmacy. But with so many states legalizing marijuana for medical use, more dispensaries are opening regularly, and some states will not want to relinquish tax and fee revenue if a federal law is passed to legalize medical use. This may require a new approach toward dispensing. Perhaps, dispensaries will handle recreational use while pharmacies dispense true pharmaceutical products. In any event, that battle is coming.

“There is an awful lot of exuberance right now, but the market is so fractured in so many ways. Can the states and the federal government see eye to eye? And there are unsubstantiated medical claims, but regulatory oversight is unresolved because the FDA is uncertain what to do,” said Darshan Kulkarni, an attorney who specializes in regulatory law. “This is a market that will definitely grow, but it’s going to take some time to mature.”

This confusion raises a vexing point.

Since there is no federal law to alter the current dynamics, state law will continue to set the tone, unless or until the FDA attempts to assert itself and regulate CBD products. To hash out the possibilities, the FDA held a public meeting at the end of May to gather information, but any decisions are unlikely for months, especially with a new interim commissioner in place.

There is another important aspect to this uncertainty. Not surprisingly, more people are using CBD products, but there is no way of knowing the extent to which any of them work. And this matters because there may be information that regulators ought to have in order to paint a fuller picture about the safety and efficacy of compounds derived from the marijuana plant. Keep in mind that there

are dozens of molecules in the plant and most have not been defined scientifically.

“The problem is that state legislation may simply become a placeholder for legalization,” said Peter Pitts, a former FDA associate commissioner, who heads the Center for Medicine in the Public Interest, a think tank that is funded in part by the pharmaceutical industry.

“Meanwhile, to my knowledge there’s no state level database of medical outcomes gleaned from the use of medical cannabis. It’s all anecdotal – patient by patient and doctor by doctor – and that’s a missed opportunity. We’re not collecting data that could be useful in the broader health conversation that could help to inform the FDA. It’s trending like a dietary supplement. The lack of data is not going to advance our knowledge and help the FDA expand the use of medical cannabis when companies seek approvals. I think the states need to start looking at the issue beyond tax revenue to see how they can capture clinical outcomes data.”

One physician who prescribes medical cannabis for her patients verified this view. Dr. Lynn Parodneck, who was trained as an obstetrician and gynecologist, but now practices community-based medicine in Bedford, NY, a suburb of New York City, has prescribed CBD products to more than 600 patients over the past three years. She has state certification to do so and believes the products are proving useful to patients, but she also acknowledged that there really is no way to know for sure.

“I can’t vouch for long-term efficacy because medical marijuana is new – there are no long-term studies. So you have to go with empirical clinical evidence. It’s all we can do. We don’t know if there will be poor outcomes,” she said. “Research has been done in other countries. If you Google and look for MS and medical marijuana, for instance, you can get a lot of results, which look good. There is research that has been done in places like Israel and Germany. And there are clinical trials in progress now with better quality products. But we don’t have answers all the time.”

And here is yet another point to consider. Under current law in the US, any research on a cannabis product that is conducted in the country must use research-grade cannabis from the only

permitted supplier, which is the University of Mississippi, where the pharmacy school has a marijuana program. This is because the DEA believes marijuana should be a tightly controlled substance.

Such disarray can appear daunting for anyone looking to start a company or hatch a new business line. There may be growing social acceptance and easy access to financing, which is enough for entrepreneurs to dive in. But for some pharmaceutical industry veterans, the current environment still falls short of what some might think of as a reliable market.

“There is another point to consider, which is that a lot of companies don’t have GMP (good manufacturing practices) and quality control and quality assurance processes in place,” said Robert Davidson, CEO at Cure Pharmaceuticals, which has developed a film technology for delivering cannabinoid medicines. “There’s a lot of money going into this area, but to a certain extent, it’s a dangerous and scary marketplace. We need regulators to step in.”

Where Is Big Pharma?

This may help explain why the world’s largest drug makers have, so far, shied away from medical cannabis, or at least are not making much noise about any plans to enter the market right now, either through in-house research or a splashy deal.

The notion of developing a new type of product that can potentially combat any number of widespread ailments is alluring. This is the sort of opportunity that drug developers and marketers live for. But even though GW Pharmaceuticals may have helped set the mold for adoption – in the US and elsewhere – the unsettled regulatory environment breeds caution. Rather than jump in with sizeable investments, the larger players could just as easily sit back and wait for the right moment to strike an alliance or simply buy a company outright.

“I think that there are two possible explanations,” said Phil Nadeau, a biotechnology analyst at Cowen & Co. “One is that there is work going on at big pharma, but we just aren’t aware of it yet. Pharma often doesn’t disclose as much about early stage programs as biotech. So, it is possible that there are early stage programs that we just haven’t found information about. The second would be that,

pharma is letting smaller companies do the early work and create the drugs and markets. Once there is success, perhaps pharma will swoop in to pick off some of the programs or companies.”

For now, the big drug makers are largely expected to sit on the sidelines a while longer, although as more regulatory questions are settled, the market should start to look more enticing. Even so, the prospect of pouring money into research or snatching up smaller players is not likely to occur quickly, despite the exuberance surrounding medical cannabis.

There are a few factors at work. For one, a certain amount of common sense dictates that the tried-and-true strategy of waiting to scoop up smaller and more nimble companies after they have generated innovative and promising products has merit. Not only does this buy time while regulators sort out their next steps, it also offers an opportunity to better assess clinical test results and, importantly, valuations. Given the fast pace of events surrounding medical cannabis, it is hardly surprising that the stock chart for the 20 companies comprising the Marijuana Index has resembled the proverbial roller coaster over the past year.

“This market has been a little bit like the dot.com bubble,” said Vincenzo Ciampi, executive director of strategic products at Sandoz Canada, which reached the deal with Tilray. “I think right now, we’re not going to see a lot of pure play pharma companies buying cannabis companies. The valuations are so high that the cost to buy them versus the revenue they generate doesn’t make any sense. Pharma companies tend to be prudent and conservative until there is clinical proof. For now, they won’t be loud about cannabis, but eventually, we’ll see more visible plays. Although I think that if pharma companies are smart, they will do some of their own development work.”

Just the same, the agreement between the two companies was a clear signal that big drug makers are, indeed, eyeing the market, especially since Tilray is one of the larger, more established players. Based in Canada, Tilray sells products in a dozen countries and also has operations in Australia, New Zealand, Germany, Latin America and Portugal. It was also the first licensed producer in North America

to obtain GMP certification that met European Medicines Agency standards.

At some point, the company may jointly develop new medical cannabis products, but for the moment, the deal is mostly about marketing and distribution, although a key piece involves developing programs to educate physicians and pharmacists, even though medical cannabis is not yet permitted to be sold in Canadian pharmacies. Nonetheless, Ciampi said this would eventually change and creating awareness now would be crucial to driving sales later.

Education Is Key

“Teaching doctors something new is difficult,” said Ron Lipsky, manager of business development and international relations at MGC Pharmaceuticals, which emerged from the Israel medical cannabis industry and is targeting the European and Australian markets. “It takes a lot of effort and incentive, and that’s hard to do right now with something that is not taught in medical school. Yes, you have some doctors in the US prescribing, but there is really a hole in the knowledge and years of medical science that requires catching up. The plant is misunderstood and the testing must be done.”

What remains unclear is the extent to which the myriad efforts will hit pay dirt, who will come to dominate the market and when the barriers to greater growth will start falling.

“There is plenty of money available to invest in companies that want to go down the FDA route, and you need that for well-controlled, double-blind studies to show efficacy and safety at appropriate doses,” said Armando Anido, CEO of Zynerba Pharmaceuticals, which is testing a product for Fragile X Syndrome, a rare inherited disorder that affects cognitive development. “We’ve raised more than \$130m over the last four years. The problem is that a lot of companies are not truly defined right now and not really evaluating compounds in a scientific fashion. And those companies that do have that ability need to see a pathway. But it is coming.”

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Comments:

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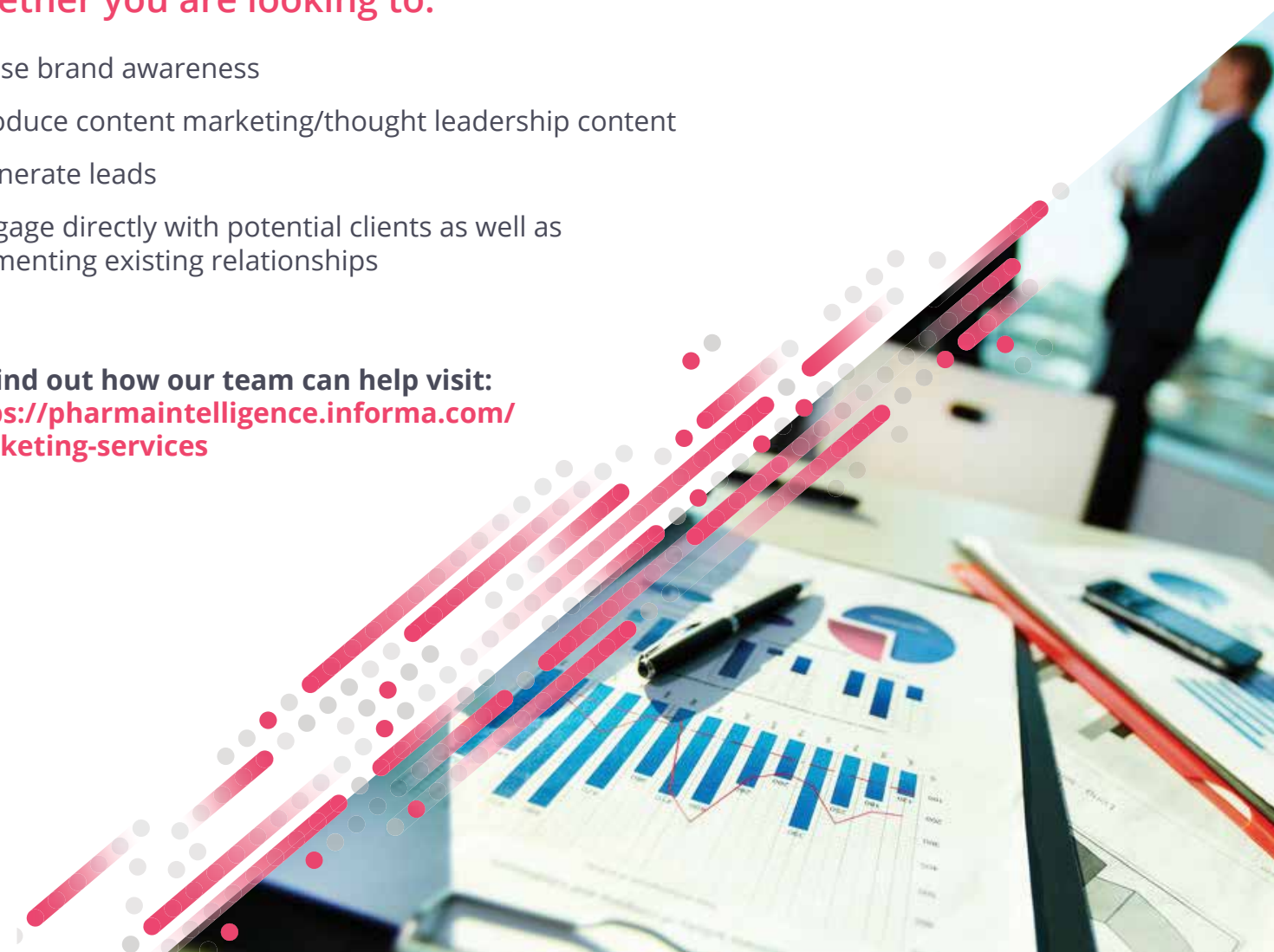


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Is A Universal Flu Vaccine Still A Lifetime Away?



Influenza is a wily foe. It shows up each winter having taken a slightly different guise to outwit our existing immune defenses, but always keeps up its sleeve an ability to shapeshift to an entirely form that could crash straight through them.

BY ALEX SHIMMINGS

The best defense against flu is an annual vaccine, and these have been available for more than 60 years. But current offerings are less than ideal.

The appeal of a so-called universal vaccine is clear, and the fact that it does not already exist speaks to the difficulty of developing one.

As with all significant medical advances, the scientific obstacles are just the start...

Flu manages to be quotidian yet cast a shade over our collective consciousness – the 100 years that have passed since the Spanish Flu pandemic infected about one third of the world’s population and killed at least 50 million people have not banished its specter.

A century on and we rely in constant vigilance and regularly updated flu vaccines to keep up with the virus, which even in a normal year can kill up to 650,000 people. Despite pandemic vaccine preparedness plans, what we still do not have is a vaccine that is truly effective and for lasts for longer than a single flu season.

The appeal of a so-called universal vaccine is clear, and the fact that it does not already exist speaks to the difficulty of developing one. But there are plenty of parties up for the task: pharma, biotech, high-profile academic centers and government authorities are all collaborating in a number of consortia and initiatives to tackle the problem.

The process is likely to go in fits and starts. A number of biotech have candidates in the clinic approaching the Phase III stage, with their sponsors hopeful of reaching the market within the next few years. These early product candidates look to be more broadly protective than current vaccines, but they are really just stepping stones along the way to a truly universal vaccine – one that after just a few shots could protect for many years and work in a pandemic year.

Moreover, the early products will have to shoulder the burden of carving out a new regulatory path to market with agencies that are comfortable with the current flu vaccine paradigm. Experts say developing a properly universal flu vaccine will be an iterative process, one that will draw on improvements made in tandem for seasonal flu vaccines, and which could take a lifetime.

The problem facing researchers is that flu, unlike more stable viruses that were

felled by vaccines decades ago, is a constantly moving target. “It is proving extremely difficult to develop a vaccine that will be accepted and will be able to easily replace the standard flu vaccine. The virus is such a clever mutator – it’s a real challenge chasing it,” explained Russell Bassler, senior vice president of research & development at flu vaccine specialist Seqiris.

Clever Mutator

Seasonal flu viruses circulate the globe each year, sweeping through each hemisphere during its colder months and lingering around the equator. There are four types of flu virus, labelled A to D (see box for WHO definitions), but it is only types A and B that are of concern for humans and, in pandemic terms, only influenza A is the malefactor.

Understanding flu’s mutability requires a look at the virus’s particular structural attributes. The A and B influenza virions (that is the complete infective form of the virus found outside the host cell) have a similar structure (see exhibit 1). They consist of a spherical protein shell (the capsid, made out of the matrix 1, or M1, protein) enveloped by a lipid bilayer that was taken from its previous host cell membrane. Spanning the protein capsid and its surrounding lipid bilayer can be found the M2 protein ion channels.

And tucked inside the core is the vi-

rus’s genome, comprising eight segments of negative-sense, single-stranded RNA coated by the viral nucleoprotein. These eight segments contain the code for flu’s 11 viral proteins – some encode for just one complete protein, others contain the genetic material for more than one protein. Another viral protein, NEP, is also contained within this core.

Finally, sticking out from the capsid and lipid membrane are two types of glycoprotein (a protein linked to a sugar) spikes, known as hemagglutinin (HA) and neuraminidase (NA).

There are 18 known HA subtypes and 11 NA subtypes, making possible many different combinations, and influenza A viruses are divided into subtypes on this basis: an influenza A virus with HA type 1 and NA type 2 is designated H1N2. In theory, a flu virus can come in any HA and NA combination but only H1N1, H1N2, H2N2, and H3N2 subtypes have ever circulated widely in humans.

On the face of it, influenza viruses are relatively simple and their surface proteins, particularly HA, are strongly immunogenic. That they have confounded efforts to develop vaccines offering long-term protection is down to the ease by which they can change both subtly and profoundly, which, in turn, is down to two factors. First, the virus uses its own error-prone RNA-dependent RNA polymerase to replicate and this introduces small changes to the virus during repli-

FOUR TYPES OF FLU VIRUS

1. Influenza A viruses are further classified into subtypes according to the combinations of the hemagglutinin (HA) and the neuraminidase (NA), the proteins on the surface of the virus. Currently circulating in humans are subtype A(H1N1) and A(H3N2) influenza viruses. Influenza A can be divided into two groups depending on the HA subtype where the human circulating H1 and H2 come under Group 1 while H3 is in Group 2.

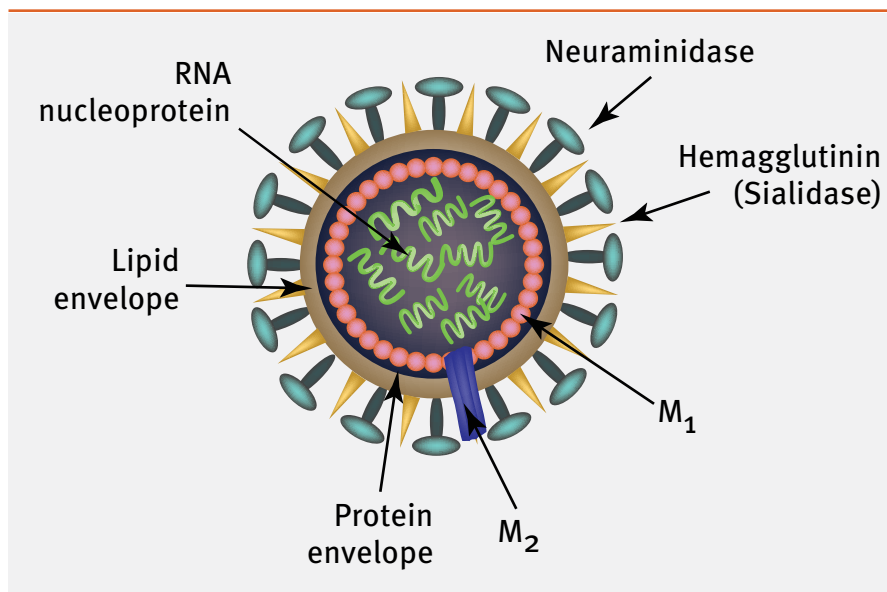
2. Influenza B viruses are not classified into subtypes, but can be broken down into lineages. Currently circulating influenza type B viruses belong to either B/Yamagata or B/Victoria lineage.

3. Influenza C virus is detected less frequently and usually causes mild infections, thus does not present a public health risk.

4. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

SOURCE: The World Health Organization

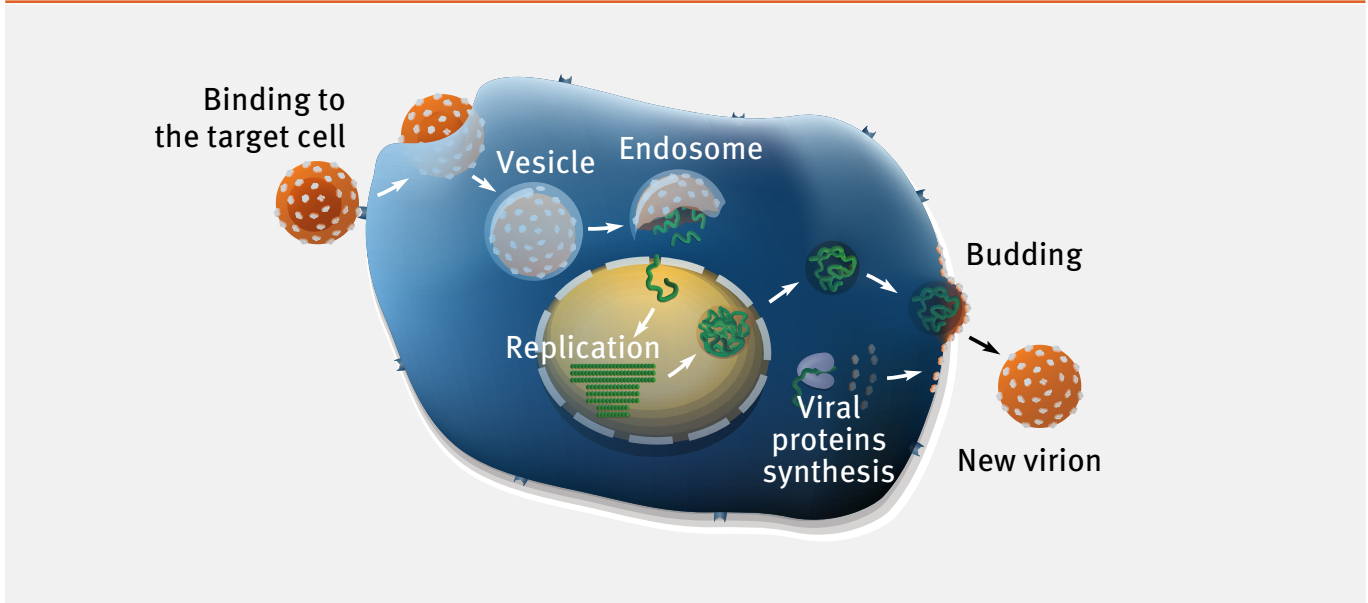
Exhibit 1
Structure Of The Influenza Virion



cation in a process known as “antigenic drift.” Secondly, the fact that its genome is spread over eight segments allows for major changes – an “antigenic shift” – to occur via a process known as genetic reassortment giving rise to the emergence of a new strain that the immune system struggles to recognize.

The more dramatic antigenic shift only occurs in influenza A because this virus type can infect many species. Aquatic birds are its natural home, but influenza A can be found in humans, poultry, pigs, horses and dogs among others, whereas influenza B only really infects humans (and seals), lessening the risk for cross-species reassortment necessary to produce an entirely new pandemic strain. The emergence in 1997 of an avian H5N1 strain able to infect humans with

Exhibit 2
Influenza Virus Replication Cycle



a 60% mortality rate raised fears of a pandemic if it were to change to become easily transmissible from person to person while retaining its virulence, and prompted improvements in pandemic preparedness plans.

Reassortment happens when two different influenza viruses co-infect a cell; during the infection process, the viruses' RNA is uncoated from the capsid before it moves inside the cell nucleus where it is replicated (see exhibit 2). The new RNA segments are exported back to the cell's cytoplasm where new viruses are built using a mix of the parent viruses' RNA segments and – voilà – a new strain buds out of the host cell. The A(H1N1) 2009 “swine flu” pandemic strain, for example, was a reassortant of avian, human and swine influenza viruses.

For unknown reasons, the severity of disease caused by pandemic strains varies – swine flu was less lethal than Spanish flu – but the new virus will enter seasonal circulation: the 2009 H1N1 pandemic virus has been widely passing round the world since and is now established in humans as a seasonal influenza virus.

Defenses Lacking

The best defense against flu is an annual vaccine, and these have been available for more than 60 years. But current offerings are less than ideal. Your annual flu shot will not protect against an entirely new

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Advances in influenza virology, immunology and vaccinology make the development of a universal influenza vaccine more feasible than a decade ago.

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pandemic strain, it will not protect you for more than one season, and it is not even guaranteed to work, although it might reduce the severity of your symptoms.

The annual vaccines protect best when they are well matched to the viruses circulating but even then they are not totally effective: the effectiveness of seasonal influenza vaccines ranges between 10-60%, with older people faring worse.

Vaccine mismatches occur despite the great deal of effort expended in trying to determine the best strains. The World Health Organization continuously monitors the influenza viruses circulating in humans via its Global Influenza Surveillance and Response System and updates the composition of influenza vaccines twice a year for the northern and southern hemisphere influenza seasons, and guides countries in tropical and subtropical areas on which vaccine formulations to use.

For many years, the WHO recommended the three most representative virus types in circulation (two influenza A subtypes and one influenza B virus), but since the 2013-2014 northern hemisphere influenza season, it has added a fourth component – a second B virus – to support quadrivalent vaccine development and broaden protection.

But choosing to any great degree of certainty is near impossible. The viruses must be picked months in advance so that

manufacturers have time to produce them, which allows time for the viruses to drift, a problem that is particularly pronounced for influenza A. This drift is compounded by that which occurs (particularly with H3N1 influenza A viruses) when the viruses are grown in the eggs used in the manufacture of most vaccine products.

What To Do?

The scale of the problem is being matched by a comprehensive approach to getting to a solution. The US National Institute For Allergy And Infectious Diseases (NIAID), part of the National Institutes of Health, has made one of its highest priorities the development of a universal influenza vaccine that would provide long-lasting protection against multiple strains of the virus, including strains with the potential to cause a pandemic. In June 2017, the NIAID convened a workshop that gathered scientists from academia, industry and government to develop criteria for defining a workable universal influenza vaccine, to identify the knowledge gaps, and work out research strategies for addressing those gaps.

The result was the February 2018 unveiling of its strategic plan for developing a universal influenza vaccine. “Advances in influenza virology, immunology and vaccinology make the development of a universal influenza vaccine more feasible than a decade ago,” it said.

It will require a coordinated and iterative approach that takes into account recent developments in vaccinology that are coming on the back of advances in structural biology, genomics and protein design. Broad collaboration and coordination in many disciplines and involving government, academia, philanthropic organizations and the private sector will be vital to achieving the goal of developing a universal influenza vaccine, it said.

In the NIAID’s eyes, a universal flu vaccine should be at least 75% effective; it should protect against group 1 and 2 influenza A viruses; have durable protection that lasts at least one year; and be suitable for all age groups.

Research should focus on three key areas:

- improving the understanding of the transmission, natural history and pathogenesis of influenza infection;

Exhibit 3 Potential “Universal” Vaccines In Development

COMPANY/ VACCINE	VACCINE DESIGN	DEVELOPMENT PHASE
BiondVax Pharmaceuticals’ M-001	Nine epitopes from three viral proteins, including five from hemagglutinin, three from nucleoprotein, and one from the external matrix protein M2 with a Montanide ISA 51 VG adjuvant	Phase III
hVIVO/Imutex Ltd/ SEEK Group’s Flu-v	Six conserved epitopes from viral proteins, including two from nucleoprotein, two from the matrix 1 protein, one from the matrix 2 protein, and one from the viral polymerase	Phase II
Vaccitech’s MVA-NP+MP1	Modified Vaccinia Ankara encoding nuclear protein and matrix protein 1	Phase II
FluGen	M2SR vaccine utilizes a proprietary M2 deleted, single replication (M2SR) influenza virus	Phase II
Compugen	Influenza A cross-subtype H1+H3+B antigens	Preclinical
TechnoVax, Inc	(Universal) virus-like particle (VLP) based influenza	Preclinical
Pharmenterprises	Intranasal universal influenza vector vaccine	Preclinical
EpiVax	T-cell epitope-based universal vaccine	Preclinical
Blue Water Vaccines, Inc.	Highly immunogenic epitope of limited variability in the head domain of the H1 HA	Preclinical
Novo Medi Sciences	Types A and B vaccine	Preclinical
Emergent BioSolutions	Injectable Nanoparticle Universal Influenza Vaccine	Preclinical
Emergex Vaccines	Universal and pandemic influenza vaccine based on gold nanoparticle carrier system technology (Emergex vaccine technology)	Preclinical
Epivax	T-cell epitopes	preclinical

SOURCES: Datamonitor Healthcare; Pharmaprojects | Informa, 2019

- precisely characterizing how protective influenza immunity occurs and how to tailor vaccination responses to achieve it; and
- supporting the rational design of universal influenza vaccines, including designing new immunogens and adjuvants to boost immunity and extend the duration of protection.

The NIAID sees this being achieved stepwise. Advances in science and technology will produce vaccines that progress up the universality scale from the current strain-specific to a subtype-specific vaccine (covering all strains within a single HA subtype (e.g. H1), then moving to a vaccine that covers multiple subtypes within one of the groups (e.g. H1/H5/H9), then a pan-group vaccine covering all group 1 or 2 influenza A vaccines, before achieving an all-influenza A virus vaccine (with or without influenza B viruses).

It said targeted, incremental advances in vaccine design (e.g. inclusion of additional antigens or adjuvants) should help improve seasonal influenza vaccine effectiveness, as well as inform efforts to achieve a universal influenza vaccine that confers broad, durable protection against multiple influenza viruses, and reduce the need for annual vaccinations.

New Ways Of Tackling Flu

Researchers are exploring a range of tactics. Improvements in cell culture technology are allowing vaccines to be produced in mammalian cells lines, which should remove the need to adapt the flu strains so they can grow in eggs and thereby make them a closer match, are ongoing along with the development of new adjuvants to boost the humoral (antibody) response.

The broader vaccine candidates currently in the clinic are aiming at different chinks in the spiky ball’s armor, seeking to target parts of the virion that do not change so much from season to season.

The flu virion’s HA spikes on the outermost part of the virion look, on closer inspection, more like long-stemmed mushrooms, and it is to the mushroom’s cap – the part most prone to change – that current seasonal vaccines elicit an immune response. But where the caps may morph, the stems stay more or less the

**Exhibit 4
mRNA Vaccines In Development**

COMPANY	mRNA VACCINE APPROACH	DEVELOPMENT PHASE
Moderna Therapeutics	Nucleoside-modified mRNA	Phase I
CureVac AG	Unmodified mRNA	Preclinical
BioNTech Pharmaceuticals/Pfizer	Unspecified	Preclinical

SOURCE: Pharmaprojects | Informa, 2019

same, making them a much more useful target for new vaccines.

There are other conserved potential targets too, including NA, the part of the M2 ion channel that sits outside the membrane (i.e. its ectodomain, known as M2e), and the internal viral proteins such as NEP. “The problem is identifying which parts of the virus we can target that are maintained between these drifting strains let alone the big change that might occur with the next pandemic,” Bassler said.

The main vaccine candidates with industry input currently in the clinic are looking at a mix of these approaches (see exhibit 3).

There are problems with some of these approaches. For a start, the HA stems are poorly immunogenic and do not elicit very strong neutralizing antibodies, and even then, they can change after many years, Bassler said. There are hints that there is more stability with the N1 and N2 nuclear proteins, but again their ability to generate long-lasting immune response has been less than ideal.

mRNA Promise

Another research angle is to use new technology to produce better vaccines, whether against old or new targets. Early in development are some mRNA vaccines using investigational technology widely being explored in cancer that promises to produce cheaper as well as safer vaccines more quickly than traditional methods.

Rather than introducing inactivated virus or viral protein antigens to provoke an immune response, priming the immune

system to spring into action if exposed to the real pathogen, these vaccines work instead by introducing the genetic code – an mRNA sequence – for the desired antigens. The host cell then translates the messenger RNA strand to produce the antigen protein which is presented on the cell surface where it can be recognized by the immune system in a way that mimics natural infection more closely.

Safety advantages over current offerings include the fact that RNA is non-infectious, does not integrate into the genome and is degraded by normal cellular processes. mRNA vaccines are potentially more nimble: their production could be highly controlled and rapidly scalable without the need for eggs or cell culture systems, giving more room to respond to both antigenic drift or new pandemic strains.

Because of its enormous public health impact, influenza virus is one of the best studied virus targets of RNA vaccine research and early animal model studies suggest that they may be better at eliciting an immune response that currently used inactivated virus vaccines. Several companies have mRNA vaccine candidates in development, although not all are specifically universal candidates (see exhibit 4).

One indication of their promise, both for seasonal flu and for universal vaccines, is interest from big pharma. The BioNTech product last year caught the attention of Pfizer, which paid \$120m up front in a collaboration deal to develop mRNA-based vaccines for flu.

Immune Responses Key

Ultimately, however, the secret to cracking the truly universal flu vaccine will most likely lie in a combination approach that also looks at the problem from the perspective of how the host's immune system reacts to a flu infection. For some pathogens, like hepatitis B, scientists know the exact type of immune response needed to provide durable vaccine protection, but the ever-changing flu is a different prospect.

Research here is intensifying. In October 2017, the global nonprofit organization The Human Vaccines Project launched its Universal Influenza Vaccine Initiative (UIVI), which it described as a "first-of-its-kind program" to look specifically into the human immune response to flu.

"There are many public and private sector resources dedicated to developing new and improved influenza vaccines, but they are all primarily focused on one part of the problem – making the vaccine," said Wayne Koff, president and CEO of the Human Vaccines Project, which brings together academia, industry, governments and other nonprofits. "What makes the UIVI distinct is that we are focusing on understanding the second part of the puzzle – the human immune response. We have to find out what generates an effective immune response against influenza in all populations in order for a vaccine to be maximally effective."

Starting last year, the UIVI brought together biomedical and bioinformatics researchers to begin the most comprehensive analysis of immune responses to influenza strains in populations around the world conducted to date.

And in November, the Human Vaccines

Project began a study led by Buddy Creech at Vanderbilt University Medical Center in which healthy subjects' response to a standard flu vaccine from Seqiris will be analyzed broadly. In addition to measuring the antibody response to the flu, this study differs in that it will also include a look at gene regulation, the influence of the microbiome, and other factors, such as whether sex affects immune response. The researchers will also take samples from participants' lymph nodes and bone marrow where key immune cells reside.

"The concept of the immuno-genome, of trying to understand which genes control which parts of the immune response to whatever – whether it be infectious disease or cancer – really does matter, and we now have the ability to really analyze the scientific data in a much more sophisticated way than we ever have before," said Seqiris's Basser. "We can really understand the correlation, whether it be around cellular responses, receptor expression, antibody responses or whatever it is that's going on in an immune response to a vaccine or an infection."

Regulatory Horizon Scanning

Something of this scale requires collaboration. "The strength of this huge broad group is that they bring all this expertise and power to what's being done. It's probably a par with, or maybe even more challenging than, the original human genome project – if you think of the complexity of tying genetic expression to biological responses to a variety of insults or challenges, you're probably multiplying the complexity by many fold."

As with all significant medical advances, the scientific obstacles are just

the start. A universal flu vaccine would need to clear regulatory hurdles to get to market, and these are still to be laid out.

Again, advances are expected to be incremental. Discussions have begun between industry and the US FDA but there is nothing there yet to challenge their current way of thinking, said Basser. A true universal flu vaccine would need a label that says it works across multiple strains over several years after giving one dose, and that would need to be proven in trials. "There's certainly a lot of furrowed brows when we speak to people around how would you get a label for universal."

The first of the more broadly protecting vaccine candidates coming over the horizon could be with the regulators in five years' time. These, plus the ongoing improvements in cell technology, adjuvants and mRNA vaccines, are moving "the dial a little bit, upon little bit, upon little bit," Basser said.

In the meantime, they will benefit the current anti-flu arsenal, and each step forward combined with the information that will come out of the UIVI initiative will help scientists get closer to the ultimate goal of a properly universal vaccine, one that protects against all strains with just a few vaccinations over a lifetime.

How long this will take is anyone's guess. "I don't think in my lifetime to be honest," said Basser. "Most people think it's going to be a long, hard grind from here on in." ❁

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Manufacturing Cures: Infrastructure Challenges Facing Cell And Gene Therapy Developers



As more regenerative medicine products approach clinical testing and commercialization, stakeholders in the field are increasingly pressed to address substantial challenges, including pricing and reimbursement, GMP manufacturing, clinical availability, and patient accessibility to these life changing therapies.

BY MICHAEL LEHMICKE

Products based on a biological material require special logistical considerations, both in development and delivery.

Though large pharmaceutical companies continue to show increased interest in cell and gene therapies, many current therapeutic developers are startups with limited resources.

The time for innovation and creative solutions to address manufacturing challenges for cell and gene therapies is now.

Over the past decade, advanced therapies have transitioned from academic dream to a clinical reality. With the recent approval of AveXis/Novartis AG's Zolgensma, a gene therapy for spinal muscular atrophy (SMA) Type 1, and the international approvals of Novartis' Kymriah, Kite Pharmaceuticals/Gilead Sciences Inc.'s Yescarta, and Spark Therapeutics Inc.'s Luxturna, it is clear that increasing numbers of patients will benefit from regenerative medicine therapies in the coming years.

Though this field has the potential to dramatically transform the health care landscape and treat patients who have in the past had limited or no treatment options, the shifting treatment paradigm also presents development and marketing hurdles which are different from traditional therapies. To ensure broad patient access to these transformative therapies in a timely manner, sector stakeholders must now convene to identify and address these challenges.

Logistical Considerations For Cell And Gene Therapies

In contrast to the current generation of medical products in wide use, products based on a biological material require special logistical considerations, both in development and delivery. Products that rely on biological starting material have shorter shelf lives, greater temperature sensitivities, and increased complexity and cost related to purity and identity testing.

In addition, the supply chain for managing these new products is incredibly complex. As the demand for cell and gene therapies increases, therapeutic developers must

contend with limitations in the supply of starting and ancillary materials involved in the production of these therapies.

In the case of gene therapies, viral vectors – which make up the delivery method of 80% of gene delivery-based therapeutics currently in clinical development – are expensive and time-consuming to produce and characterize. For certain cell therapies, the production of appropriate cell lines for the development of therapies can be limited by the quality and quantity of the starting material. In many cases, researchers can only obtain a small number of cells which then require weeks of labor to cultivate and expand to a sufficient number for development of the therapeutic product to begin.

Though large pharmaceutical companies continue to show increased interest in cell and gene therapies, whether through in-house development, in-licensing, or partnering deals, many current therapeutic developers are startups with limited resources. Often, these developers rely on a single source supplier to provide critical equipment and materials, which introduces additional risk and potential bottlenecks in the development process.

The supply chain for autologous cell therapies is further complicated. These therapies rely on the patient's own cells, which are collected during an initial appointment at a clinical facility. They are then purified, genetically or chemically modified, and expanded in order to produce the desired therapeutic effect before they are re-administered to the patient. This process typically takes weeks, relies on seamless transfer and management of materials between clinical sites and manufacturers, and delivery timelines are easily disrupted by patient-specific issues, resulting in delayed or lost opportunities for treatment.

In addition to potentially increasing the time it takes to administer these therapies to patients, the personalized nature of these autologous therapies also means that developers are unable to take advantage of the economies of scale that are created when manufacturers of traditional pharmaceuticals produce large quantities of a product. The quality of the final product is strongly related to the biology of the individual patient's cells. Lot failures can commonly occur due to quality issues

such as a failure of the cells to expand, or poor response to *ex vivo* modifications.

Post-approval, cell and gene therapy manufacturers often run into another hurdle: supply and capacity planning. Demand for a specific product may be difficult to determine. This is particularly true for therapies for orphan indications, where the number of infants born or patients diagnosed with a disease, as well as the overall patient population, can be extremely variable. Additionally, it can be difficult to predict uptake post-approval, particularly when pricing is contentious. This can result in an acute disconnect between available resources for therapeutic development and patient need, with both parties suffering the ill effects.

Finally, differences in Chemistry, Manufacturing and Controls (CMC) requirements from country to country and duplicative processes for testing, reporting, and clinical submissions can place an undue burden on developers. The cost of manufacturing products for clinical trials and commercialization post-approval is particularly challenging and risky for small companies, which is exacerbated by international uncertainty. Ensuring that there is sufficient international convergence on regulatory and clinical requirements will allow patients to access safe and effective products without unnecessary costs and delays.

Increased Urgency In Addressing Manufacturing Challenges

The time for innovation and creative solutions to address manufacturing challenges for cell and gene therapies is now. Over the next decade, there will be a considerable increase in the number of patients who require and qualify to receive these transformative, increasing the urgency for implementation of novel methodologies. According to data maintained by ARM, of the 1,060 ongoing clinical trials in regenerative medicine worldwide, there are 80 cell and gene therapy trials in Phase III, suggesting that the number of approved products on the market will soon increase significantly, and with that, patient demand. The US FDA said in a January 2019 statement that by 2025, they expect to be approving 20-25 regenerative medicine products annually. The EU is also preparing for the coming

THE RISE OF REGENERATIVE MEDICINE

Regenerative medicines, including cell and gene therapies, augment, repair, replace or regenerate organs, tissues, cells and genes within the body. These therapies have the potential to provide a profound and durable response – often with just a single administration – for patients with a diverse array of serious diseases and disorders. Unlike traditional drugs, these therapies focus on treating the underlying cause of diseases and disorders, rather than focusing on chronic care.

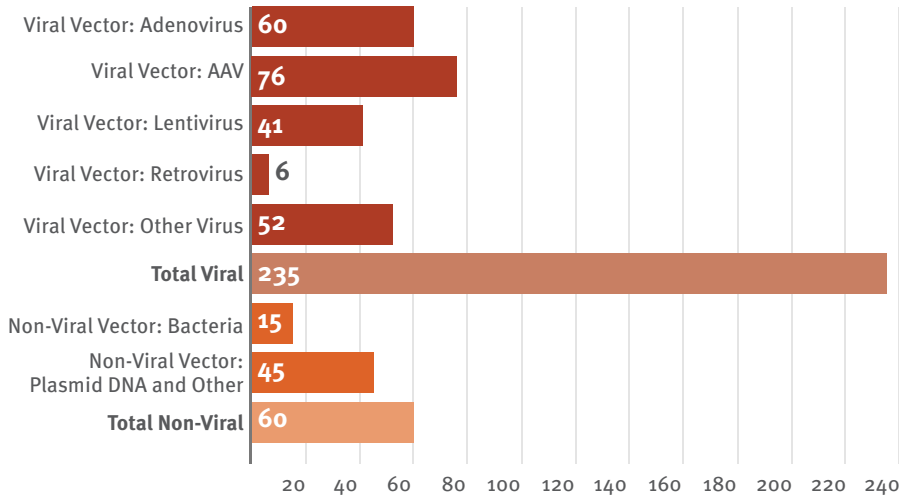
This field is undergoing explosive growth. As of the first quarter of 2019, the Alliance for Regenerative Medicine is tracking 917 regenerative medicine therapeutic developers worldwide including companies active in gene therapy, cell therapy and tissue engineering. 2018 was a watershed year for regenerative medicine financings, with \$13.3bn raised worldwide, and this investment energy continues in 2019. The sector already raised \$2.2bn in Q1, with \$2.1bn raised by gene therapy developers and \$823m raised by cell therapy developers.* In addition, the global clinical pipeline is robust, with 1,060 clinical trials currently ongoing across a variety of indications utilizing regenerative medicine technologies.

**Total amount represents sector-wide figures; some companies utilize technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups. Figures do not include M&A transaction totals.*

wave; at ARM's April 2019 Meeting on the Mediterranean in Barcelona, European Medicines Agency director general Guido Rasi announced EMA expects to approve 10+ products annually in the near future.

Approved products are not the only drivers of demand for cell and gene therapies. The clinical trial pipeline is

**Exhibit 1
Viral And Non-Viral Vectors In Gene Transfer Clinical Trials**



SOURCE: Alliance For Regenerative Medicine

increasing as well. The FDA is preparing to receive 200+ INDs each year for clinical trials in regenerative medicine. Targeted enrollment in current ongoing clinical trials worldwide is nearing 60,000. By 2030, the MIT NEWDIGS consortium predicts that more than 500,000 people will have been treated with cell and gene therapies in the United States alone.

This increase in demand is partially driven by a shift in focus from monogenetic orphan indications to “mass market” indications with larger patient populations, such as cardiovascular conditions or central nervous system disorders. The first gene therapy for critical limb ischemia, AnGes’s Collatagene, has already received approval in Japan and is currently in clinical trials in the U.S. A number of other indications with large patient populations and correspondingly considerable impact on health care systems are also experiencing increased clinical interest. Currently, there are 13 ongoing cell and gene therapy clinical trials in critical limb ischemia; 13 in diabetes and related complications; 11 in myocardial infarction; nine in stroke; eight in Parkinson’s disease; and five in Alzheimer’s.

In addition to the increase in available products and the size of patient populations, cell and gene therapy developers are also striving for shorter development timelines, driven by the availability of expedited approval pathways, including RMAT, Breakthrough, and Fast Track des-

ignations in the US; PRIME designation in the EU; and SAKIGAKE designation in Japan. These designations help to ensure that patients are able to access innovative therapeutics as efficiently as possible, but shorter timelines mean that developers must begin to plan their large-scale manufacturing strategy early on in the development process – sometimes before they even begin to dose patients – or risk collapse post approval.

As these therapies have begun to come to market, investors have taken an increased interest in how companies plan on handling large-scale manufacturing. On a panel on the investment outlook at ARM’s March 2019 Cell & Gene Investor Day, Aquilo Capital Management Principal Patrick Rivers commented that the issue and challenge of “manufacturing becomes questions one, two, and three” when making investment decisions. Sector stakeholders will need to work to provide innovative solutions to manufacturing hurdles in order to maintain investor interest and foster the furthered growth of the sector.

What Are The Solutions?

Many therapeutic developers in the cell and gene therapy space have turned to professional manufacturing organizations, both CMOs and CDMOs, to help develop and manage their manufacturing programs. Startups and small therapeutic developers, who may not have the resourc-

es to manage manufacturing in-house, may particularly benefit from outsourcing strategies. Larger CMOs and CDMOs are often able to take advantage of economies of scale, where smaller developers cannot, and their specialized knowledge and equipment can help to streamline and standardize the manufacturing process.

However, outsourcing can have drawbacks. The developer may have less oversight over the manufacturing process, and disruptions at the CMO or CDMO can create bottlenecks for the developer – particularly if they rely on a single CMO or CDMO to fulfill their needs. In addition, the majority of current generation regenerative medicine products are highly specialized, requiring bespoke components and specifically trained staff. The traditional CMO model struggles to accommodate such unique and non-standard technology approaches, which can result in delayed tech transfer and negatively impact the developer and their patient population.

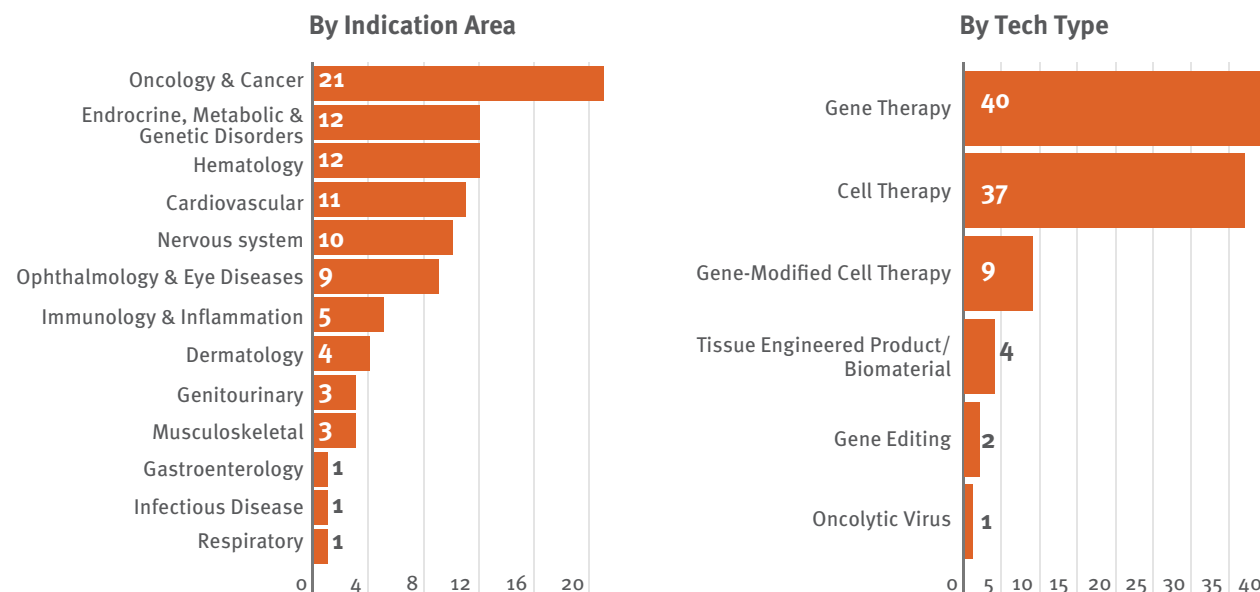
Because of this, many therapeutic developers are planning to handle their manufacturing in-house, or with a combination of in-house and outsourced services. While this approach may be more difficult for startups and can introduce new complications for developers to achieve the time and cost savings provided by large-scale manufacturing set-ups, it does provide additional oversight and quality control.

The increased interest in in-house manufacturing options has recently led to a balloon of M&A activity, with CMOs and CDMOs becoming attractive acquisition targets. In the past year, Novartis acquired CellforCure, a French CDMO, to expand their manufacturing capabilities in the production of their CAR-T therapy Kymriah; Hitachi acquired apceth to increase their manufacturing capabilities in Europe; Thermo Fisher paid \$1.7bn to acquire CMO Brammer Bio; and Danaher paid \$21.4bn to acquire GE Healthcare. Manufacturing, and pinpointing the associated solutions has become an attractive, if challenging, business.

Additionally, as the science in this field advances, we may see other solutions that address some of the current issues with manufacturing. An increasing number of cell therapies are allogeneic or “off-the-shelf” cell therapies. Because

Exhibit 2

Expedited Approval Pathway Designations By Indication Area And By Technology Type



SOURCE: Alliance For Regenerative Medicine

these therapies are not personalized like autologous cell therapies and do not require the starting material to come from the patient being treated, the manufacturing and distribution process reaps the benefits from economies of scale, and the therapy is able to be administered to the patient much more quickly. In gene therapy, increased interest in next-generation non-viral delivery methods – including nanoparticles, nanospheres, transposons, electroporation, excitation, and others – may partially alleviate the need for viral vectors, which are expensive and time-consuming to produce.

With this said, it should not be solely the responsibility of companies to alleviate manufacturing hurdles. Regulatory agencies across the globe are contributing to the work to address challenges in manufacturing. The US FDA released several draft guidances relating to CMC and manufacturing in March 2018 (finalized in March 2019) and December 2018, which have increased clarity for developers.

Also, both the FDA and EMA have expressed interest in increasing regulatory convergence, which would streamline the process of expanding access to therapies in additional countries. This common interest in novel regulatory methodologies has fostered deeper communication between industry and the agency around needs and

expectations, with organizations like ARM playing a key role in facilitating productive, precompetitive dialogue.

Nonprofit organizations have partnered with regulatory agencies to provide guidance on overcoming manufacturing hurdles as the field grows. The Standards Coordinating Body, an independent nonprofit 501(c)(3) organization that spun out of an initiative of the Alliance for Regenerative Medicine’s Science & Technology Committee, is working to promote the coordination of standards activities, including those involving manufacturing, across the regenerative medicine community to accelerate standards advancement. ARM is currently developing the “A-Gene” and “A-Cell” projects, intended to create a case study-based reference guide on the best practices for the development of gene therapies and cell therapies, respectively. An expert industry team, including 47 contributors from 31 member companies, will address key topics in the development and manufacturing of cell and gene therapies, including comparability, critical quality attributes, the product life cycle, the development and use of standards, regulatory implications, and others. The A-Gene team anticipates publishing their results by the first quarter of 2020; the A-Cell project is expected to publish in late 2020.

The Future of Manufacturing For Cell And Gene Therapies

While we have seen considerable improvements to the manufacturing process in recent years, there are still hurdles to overcome. As the regenerative medicine sector continues to grow, and cell and gene therapies are made available to an increasing number of patients, the field will experience an increased need for innovative solutions to manufacturing and infrastructure challenges. It is likely that a combination of efforts – strategic business investments, novel manufacturing models, advances in the science cell and gene therapy, the work of regulatory bodies to promote clarity and convergence in CMC requirements, and cross-sector coordination focused on the improvement of manufacturing processes – will result in significant improvements in the manufacturing environment for cell and gene therapies in coming years.

Cell and gene therapies have the potential to drastically transform our health care systems and improve the lives of hundreds of thousands of patients across the globe in the relatively near future. Stakeholders must now come together to surmount the challenges of manufacturing cell and gene therapies in order to improve access to and fully recognize the promise of regenerative medicine. ❁

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LEADING FROM THE LAB:

MIT's Robert Langer On The Converging Science Of Drugs, Devices And Delivery



Ten years after our first encounter with MIT's Robert Langer, In Vivo sits down with the polymath professor – arguably the most inventive and prolific life scientist of his generation – to identify key challenges in medicine.

Photo Credit: Bachrach

BY WILLIAM LOONEY

Langer's lab at MIT is a wellspring of entrepreneurial initiative, providing the science behind more than 100 products – drugs and devices – now widely used in clinical practice.

The Langer Lab is looking for better tools to help researchers study brain function, with a multidisciplinary effort underway involving prominent neuroscientists, engineers and biologists from MIT and Harvard.

So what? Seen as a precursor of trends in bioscience research, the Langer Lab is increasing its focus on access and delivery platforms that work in resource-constrained settings, with the Gates Foundation emerging as an important partner

In Vivo: You stand out as one of the first members of academe to demonstrate the potential in translating basic research into innovations that not only change medical practice but find success in the commercial marketplace. With a 40-year track record of founding three dozen biotech start-ups, is there an enduring fundamental behind successful entrepreneurship? What is different about creating a company today?

Bob Langer: I did not start out with an entrepreneurial mindset. As a young professor at MIT in the early 1980s, biotechnology was emerging as a distinct area of the life sciences. I was trained in the discipline of chemical engineering, which is useful in figuring how to turn a concept into a technology that will produce a desired prophylactic effect when introduced to the human body. I learned about the interdependence between chemistry, physics, biology and engineering as the building blocks for a new era of progress in drugs and medical devices. In addition, MIT as an institution had always been supportive of faculty taking an outside perspective and making academic research more relevant to real world applications. Given my knowledge in applied science, many people approached me about starting new companies (*see exhibit 1*). For a long time, I resisted the idea.

But eventually I decided I would start companies to move things out of our lab and into patients, and today I am glad I did. The impact of what has been accomplished in our lab has been magnified many times over in the clinical setting. As far as any differences between when I started over 40 years ago and today, I don't see many. If

one has the essential ingredients of a good idea, a patent, very good data, and some talented people are present, you can often start a company. The issue is one of degree. There is far more money available today than 40 years ago to help push basic research forward to the marketplace and entrepreneurship is more ingrained in the institutional culture of academia. Younger researchers are also far more open to taking a chance on an untried innovation.

Many of the 36 start-ups you helped found have attracted the interest of the big pharma majors. What is it like working and negotiating with the top players – is the entrepreneurial mindset still at odds with the cultures of big pharma?

Big pharma's interest in what we are doing has always been strong. Back in the 1980s, my lab secured grants from big pharma, who approached us with the best of intentions. Unfortunately, if a huge success didn't happen right away (and it often didn't), the commitment could flag and our partners would pull back. That was anathema to me, because innovation is rarely revealed on the first try. Even a novel premise validated with strong technology is going to encounter some problems and delays as it moves toward a marketable product. Overall, the experience with big companies has taught me that successful entrepreneurship is contingent on the funding partner having a strong internal champion for your research. With big pharma, it was never money or contract language that soured the relationship. Instead, it was bureaucratic distractions and the inability to commit to a project for the long-term.

What I have observed says a lot about the big pharma business model and how it has moved away from a reliance on pursuing R&D entirely in-house. What the companies really do well is on development validation and logistics, from clinical trials to regulatory approvals and thence to commercialization and marketing. But, as far as the basic research is concerned, you need people who are going to walk through walls to get the science right. You cannot just change course and move to the next project. This is why some small start-ups have a better track record in breakthrough early-stage research – because the choices are binary and you just won't have a business if you don't make the commitment necessary to succeed. I would not go to extremes and contend that great science can't happen in big pharma – it clearly does – but the urgency, dedication and passion-against-the-odds culture found in some start-ups is often much greater. Big companies have big agendas and it's easier to get lost in the fray.

Although your own career is an example of the benefits that come from interdisciplinary collaboration, academic life can also be contentious. Is silo thinking still prominent in the culture of most of the large research institutions in the US?

It varies – on balance it is probably still the rule rather than the exception. My personal desire is towards working across disciplines because of what I want to do. However, the physical plant of most universities reflect the silo point you are making. Our building here at MIT is fairly unique, as we have biologists and engineers working in one space. It is far more common for biologists to have a building for themselves while engineering

schools even host separate spaces for colleagues on the chemical and electrical sides of the field. Personally, I don't see taking a silo approach as bad. What we should aim for is the freedom to embrace variety and diversity in the way we pursue knowledge. I have enjoyed melding engineering with medicine but a siloed focus yields research breakthroughs too.

Another ingrained aspect of academic life is the H-index, which measures the productivity and citation impact of a scientist's work in peer-review publications. Is the "publish or perish" ethos in science giving way to the pressure to generate funding for laboratory work?

The ideal is that these two markers of achievement should go hand in hand. My aim is to achieve a balance on both measures of performance: my H-index makes me one of the top four or five of the world's most cited scientists in history; my lab pulls in on average about \$20m a year to help support our research initiatives.

I think published output can help to draw in top new research talent, which in turn gets the work we do noticed enough to hopefully fuel the financial resources necessary to develop and perhaps commercialize that idea – resulting in a product that can actually be used in the patients who need treatment. For me, it is all about having an impact, in ways that are often not evident when we began our research. I believe that rigor in research, reinforced by the citations that indicate how well colleagues regard our work, is ultimately more important than raising money. I look at money as connoting the freedom to conduct good research rather than the professional validation you ultimately take from peer-reviews.

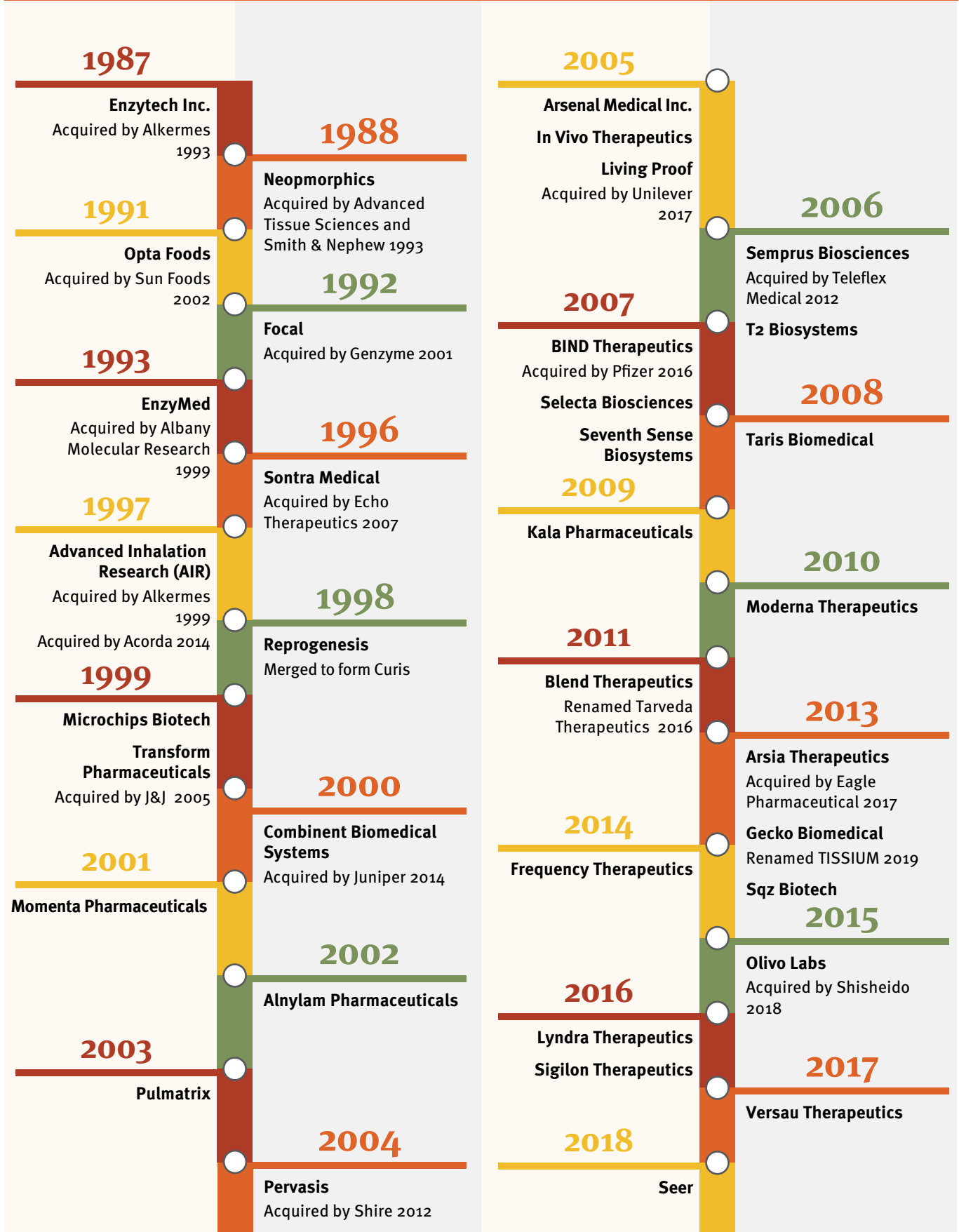
As a leading medical researcher, what in your view is the state of science today? Is biology too complex to be codified or are we on the cusp of truly transformational breakthroughs?

There have been continuous advances in our understanding of human biology since the turn of the century. Much remains to be revealed about biology and its application to medicine but significant groundwork has been laid, mainly in the form of tools like gene sequencing that took many decades to refine to where researchers now have a very sophisticated awareness of the entire human genome. Today we are finally seeing this knowledge applied to create medicines that have the potential to cure an untold number of diseases, many of which do not even have treatments.

I like to think the work we did in engineering synthetic polymers and other materials to accelerate the delivery of medicines and make devices work better has improved patients' lives. Drug delivery has come a long way; from the small molecule pill taken multiple times during the day, to the now common transdermal patch, and now to tiny particles called microspheres and nanoparticles that represent a revolution in controlled release technology. These have enhanced the potency, durability and effectiveness of a medicine against a diverse range of hard-to-treat conditions like advanced prostate cancer, endometriosis, ophthalmologic diseases, schizophrenia, type two diabetes and most recently opioid addiction.

Exhibit 1

Progress Of A Polymath: Companies Founded Or Co-Founded By Professor Robert Langer Of MIT



In addition, a new generation of drugs built on the messenger RNA protein synthesis platform have been designed to deliver their payload as nanoparticles. Moderna Inc., a biotech company founded by myself and others in 2010, is conducting 11 clinical trials on messenger RNA drugs, most of which rely on the nanoparticle technology. Delivery platforms built by bioengineering hold out the promise of greater access to novel treatments for millions of patients worldwide. There are cost savings as well: tools that enhance compliance by making it easier for patients to take a prescribed drug have a huge economic impact when you consider that non-compliance with drug therapy costs the US health care system an estimated \$300bn a year.

The Langer lab operates at “the interface of biotechnology and materials science” and is currently the largest bioengineering research lab in the world. How do you manage a group with such a broad interdisciplinary mandate and what is its role within the overall MIT research ecosystem?

The lab continues to focus on basic engineering research in a few big areas, including what we are best known for: finding new ways to deliver drugs and medical devices to improve the lives of patients. It includes our early discovery work on tissue engineering as well as the nascent technology around nanoparticles in delivering new drugs including messenger RNA. We are looking at methods to enhance the delivery of medicines or vaccines to almost every part of the body, from the brain, to skin, and the lung – all the major organs. Breaching the blood brain barrier is a key “hard problem” in science, so we are considering intensifying research in this area, given that the potential for safer, more powerful drug-based solutions is very high. It is one of the next frontiers in drug delivery.

Our other priority relates to my longstanding interest in tissue and organ engineering, an area of investigation I initiated some decades ago with Dr. Joseph Vacanti of the Harvard Medical School. The work involves study of different materials like super-biocompatible polymers and understanding how these relate to cell growth and behavior, leading to artificial organs that mimic the performance of real ones in the body.

Increasingly, our lab’s work is sparking interest from development and philanthropic organizations like the Gates Foundation, which is now working with us to create platforms and products that seek to address access problems to drugs and devices in resource-poor countries. Can we find a way to administer a high-potency drug once a month instead of every day, thereby treating more patients and raising levels of compliance? Can we create a controlled, time-released version of a pediatric medicine, powerful enough to treat or cure without any residual side-effects in small bodies? Can we develop methods to administer nutritional products or essential vitamins in combinations, thus treating the ‘whole person’ from a single pill? Are there simpler and climate-sensitive ways to improve the efficacy and administration of vaccines?

These are the questions our colleagues from Gates would like us to help resolve. Other NGOs like the Helmsley Foundation and the Juvenile Diabetes Foundation are involved in advancing our work on the artificial pancreas and “smart” insulin. Finally, we have a history with the Prostate Cancer Foundation, another

leading advocate for materials capable of delivering powerful anti-tumor therapies to patients, safely and without side-effects.

Companies are well represented on the lab’s project list as well. Novo Nordisk AS has provided us with a grant to study ways to deliver insulin orally, with a pill; Roche is interested in finding a pathway to address various precorneal and ocular barriers to stable drug delivery; and Alnylam Pharmaceuticals Inc. has supported work in creating new nanoparticles for delivery of siRNA drug targeting in patients. And, of course, there is the generous ongoing support from the National Institutes of Health (NIH) grant program, which allows us creativity in addressing many basic, long-term challenges in drug delivery in so many difficult areas, like hearing loss or replacing diseased gums through tissue engineering.

What about the people factor in making your lab so successful over the years?

This is what I am most proud about – the raw talent from so many places that has flourished here over the past four decades. Right now, we’ve got about 100 researchers active on site, with backgrounds in over a dozen different disciplines. When you go through the list of all our students and post-grad researchers, it is wonderful to see how so many have progressed into productive and meaningful roles, not just in academia but in industry and the professions as well. Nine of our lab alumni are serving as university professors at MIT, 14 at Harvard, seven at Stanford, five each at University of Michigan and Johns-Hopkins, three at Yale, and many others – and that is just in the US. All told, I estimate up to 400 of our former researchers hold professorships at top research-oriented university institutions around the world.

MIT hosted a reunion of my lab residents and students in September 2018, on my 70th birthday. I was pleased to see how many have started their own companies or served as CEOs in biotech. It was particularly pleasing to see the strong entrepreneurial bent of the group – 26 have been elected to the National Academy of Inventors, 18 to the National Academy of Engineering, and 15 to the National Academy of Medicine. Time and effort have produced perhaps the best networks of enterprising human capital ever launched out of MIT: a distinct ecosystem of talent and scientific merit that has matured to seed innovation in many fields and geographies.

Do you have any specific priorities for the Langer lab this year?

I prefer to see our priorities as a continuation of the three things we have been doing all along: (1) dream up new ideas around drug delivery and materials science, and then move them from a place where people who once said ‘this won’t happen’ will say ‘yes it will’ – in a published, peer reviewed paper; (2) ensuring that things we have already done will have a demonstrable impact on patient care; (3) and find and train the very best people in our field. This is what I was doing 20 years ago and I don’t want to change that direction.

When I am asked about our work, I sometimes emphasize the practical aspects. Through the principles we have developed over time, medicine have transitioned from a state where you could deliver only the smallest molecule for a short duration to one

where almost any payload can be delivered for whatever period of time is necessary to secure the optimal target effect. These principles are applicable to virtually every aspect of medicine, including the current preoccupation with better ways of delivering opioids without addictive effects. In fact, our lab has done much of the basic foundational work on applying polymers that led to ensuring that these medications are released slowly to minimize the addictive high and the life-threatening overdosing from use of opioids. It is rewarding to be participating, in a fundamental way, to find solutions to this contemporary public health crisis as well as others.

What do you see as the hardest challenges in medical science today?

Clearly, the blood brain barrier remains key. We still lack a complete understanding of the basic biology of the brain and how this organ is responsible for so much of what keeps the various systems of the body in equilibrium. One thing we've been doing over the past two years is finding better tools by which researchers can study brain function. Our Lab is collaborating with outstanding neuroscientists like Ann Graybiel, a fellow Institute Professor at MIT, Professor Michael Cima and other members of the MIT Engineering School faculty along with biologists from MIT and Harvard, to work jointly on this important investigatory project. It is very early, but I hope breakthroughs in brain science and the underlying causes of dementia and Alzheimer's will come from this kind of interdisciplinary effort involving these three branches of the life sciences.

As an aside, I am convinced that the research organization and funding model we have created in health and medicine through the NIH should be applied to other important challenges involving the life sciences. Climate change, for example, is a public health issue, with an impact on everything from disease incidence to nutrition and sanitation. Weather patterns leading to powerful hurricanes can cause hundreds of billions of dollars in damages, yet we do not currently have good models to help us study and anticipate these trends. We have taken on that challenge in medicines; we need the same kind of incentives that will encourage our top minds to tackle this one too.

What disease areas offer the best prospects for a short-term breakthrough that will help patients in a fundamental way?

Advanced cancer treatments continue to offer hope in many areas, and survival rates for some malignancies are on the upswing. Less noticed but of equal importance are emerging pathways to fight hearing loss, to repair the spinal cord and restore motor function, and stimulating the growth of blood vessels – in the latter case, this has major implications for wound healing, tissue implants, and resolving the vascular impacts of diabetes. What is wonderful about our system of academic research is how what was done many years ago in a lab and published for all to see can find fresh momentum as the knowledge base expands. The early work I did in the 1970s with the late Dr. Judah Folkman on tumor angiogenesis inhibitors as a possible treatment for cancer was validated 30 years later, in 2004, when researchers at Genentech Inc. won approval from the FDA for Avastin, the first angiogenesis inhibitor drug for use

in patients. Science moves slowly but inexorably toward truth. This is what I find wonderful – the hope. You just don't know what will happen but when it does the reward is incalculable.

Another challenge I see is perhaps more political than scientific – increasing access to research in areas of the world that are still developing economically and could benefit from access to new health technologies. Our lab is putting more emphasis on discoveries that address the different delivery infrastructure in developing countries. It explains the growing collaborative relationship we have with the Gates Foundation, which is taking a more direct role in financing drug, device and vaccine development.

If you were asked to address the top 20 biopharma industry CEOs and R&D leads at their private gatherings like Dolder or the Hever Group, what message might you give to them?

I would emphasize the importance of discovery research and basic research and the value that comes from the academic side of the bioscience ecosystem. Our lab at MIT has put forward for commercialization more than 100 products that create new options for patients. And the reason we have had that success is we chose to put our strength behind things that had not yet happened. We explored uncharted territory and I like to think what we invented may open whole new areas of technology and science, with applications across many therapies. This approach can potentially transform the future. Of course, companies face certain constraints. It can be hard to make a profit when the focus is several decades forward. The response to that is to ensure your culture embraces the world outside; and that your own researchers are watching what those of us in academia are doing.

Do you have a perspective on today's generation of young scientists and post doc researchers compared to when you entered the field?

The current generation is much more entrepreneurial than my own. It may be that grants from the federal research agencies are harder to get and come later than in the past. Hence there is a greater openness about taking risks to start a company. In the Internet age of high-tech, I see more confidence about believing a fresh idea will get noticed, attract financing and succeed. The level of passion and dedication is as high as it's always been. It's hard not to believe you have an impact when you see this abundance of science stretching beyond the horizon. ✨

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Comments:

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NEW SCIENCE AS A GROWTH STRATEGY: Three Dimensions To Guide The Transition From Old To New



Finding innovative ways to adapt the biopharma business model to external and internal challenges is a key competitive differentiator for today's C-suite leadership.

**BY SANSKRITI THAKUR AND
GORDON MURPHY**

Disruption is a fact of life in today's biopharma enterprise – addressing it requires first identifying the type of disruption and then building a structured response consisting of three distinct dimensions of a new approach to innovation: the science of treatment, the science of technology and the science of the expectant patient.

An expert analysis by Accenture Life Science Research, Accenture LLC, contends that a rigorous approach to R&D focused on frontier science, unmet patient needs and new health technologies, reinforced by identifiable characteristic markers or archetypes, results in investments that are not only better targeted to patients, but offer higher sustained revenues and return on investment over time.

Finding innovative ways to adapt the biopharma business model to external and internal challenges is a key competitive differentiator for today's C-suite leadership. The stark choice is to disrupt – or be disrupted. Accenture's work with numerous life sciences companies over the past few years reveals there are two typical types of disruption, each requiring a different strategic and organizational response. The first is that intuitively self-evident “big bang” disruption where a new innovation revolutionizes an entire industry and causes major and immediate change. The second is “compressive disruption” where a series of smaller innovations slowly build over time, and depending on other external factors, are often unnoticed and lead ultimately to a crisis of decreasing profits in the disrupted companies.

Our conclusion is that compressive disruption is the bigger threat to the health of the biopharma business model because it allows for complacency when what is really needed is proactive initiative and a change in mindset, both of which are difficult to implement in large organizations that tend to be resistant to change. In contrast, the response to compressive disruption demands a turnaround in basic strategy on how a company's research output – the science – is evaluated, resourced and conducted.

We call it “New Science,” where new management and operations approaches are integrated around a more focused strategy. To stem the slow decline to organizational inertia exemplified by compressive disruption, companies must establish a work culture that is relentless in generating value from every investment it makes, from the discovery phase right through to patent expiry, and involving a range of inputs that include applied tools and technology as well as the products of scientific discovery and research.

Accenture recently published a white paper, *New Science: Biopharma's New Growth Machine*, to showcase the merits of how New Science can itself be the antidote to compressive disruption by keeping companies fixated on being first to “get to what’s next” in unmet medical need – staying on the vibrant edge of science, rather than safely in that middle ground of institutional status quo. Often too much focus is given to the hottest cutting edge science, while incremental areas of growth are overlooked. This article drills down into how to approach the innovative impulse structurally, by identifying several “archetypes” that life science companies should emulate in institutionalizing New Science to generate a predictable – and progressive – gain in revenues from their biopharma investments. By applying this construct to their own operations, management can anticipate, track and assess the strategic imperatives shaped by these archetypes – and bridge that transition gap from old science to the new.

New Science: It’s More Than Cutting-Edge Technology

As a concept, New Science denotes a multitude of innovations that capture value simply by advancing the science beyond where it is today. To effectively benchmark and diagnose the industry in this context, we have split New Science into three recurrent drivers of organizational coherence and commercial success: New

Treatment Science, New Patient Science and New Tech Science. Each is defined by separate archetypes, capturing the key types of innovation which is, or has been recently, new. Exhibit 1 outlines the dimensions of New Science, and their three archetypes.

In each dimension, New Science goes beyond the latest cutting-edge therapies or trends, capturing all the incremental changes leading to improved value and patient outcomes; these are often beyond traditional clinical outcomes. The whole industry, its therapeutic areas, indications and the individual companies involved, can be assessed through these three dimensions. This allows for benchmarking and analysis, and gives the opportunity to identify areas of strength, weakness and opportunity. Importantly it enables one to redirect investment for a purpose, whether that be revenue or an unmet medical need.

As the science in the pharmaceutical industry is broken down into its constituent parts, products can be categorized by the type of science, and the type of “New.” Exhibit 2 provides an overview of the historic and projected revenues for launched products in the prescription pharmaceutical industry categorized by the dimension of science affecting the treatment or patients. Tech Science has not been included in this analysis as its application is more complex and the field is comparatively very new, but its general characteristics are summarized below.

Bridging Old And New Science: Selecting Dimensions And Archetypes

What about the conventional way of approaching science, or what we refer to as Old Science in New Science: Biopharma’s New Growth Machine? Although relatively stable in value, Old Science makes a steadily decreasing contribution to the total growth of the industry, while the future growth of industry revenues is largely driven by the introduction of New Science Products. Therefore, trade-offs must be made to navigate the span between Old and New Science.

Within New Science there is a stable proportion of revenue from New Patient Science by itself (i.e. around 6%), but the proportion of revenue from New Patient Science increases when combined with New Treatment Science (25%, or \$170bn, in 2018; rising to 29%, or a projected \$252bn, in 2022). This suggests that although using Old Science methods in new indications still retains some value, most of the growth in New Patient Science is from the combination with New Treatment Science. Therefore, we conclude there is only limited value in tackling a new patient group using standard methods, but that using new methods to tackle new patient groups could be a substantial engine for growth.

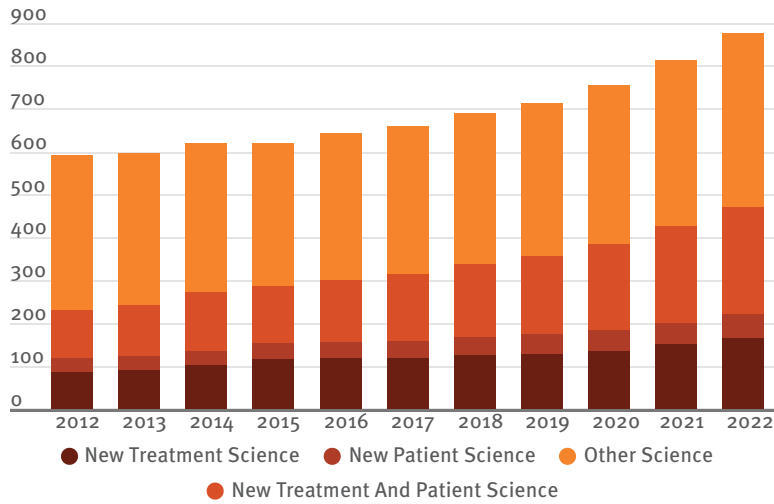
New Treatment Science by itself is slowly increasing as a proportion of pharmaceutical revenue, as well as increasing in value (\$88bn in 2012 to

**Exhibit 1
The Three Dimensions Of New Science**

NEW TREATMENT SCIENCE	NEW PATIENT SCIENCE	NEW TECH SCIENCE
<p>Scientific product advances, including new mechanisms of action, therapeutic classes, drug discovery pathways and formulations which add value to patient outcomes, as well as the more usual scientific progression into new targets.</p> <p>The dimension that triggers questions about where we should be investing for scientific novelty and for return on investment.</p>	<p>Advance aimed at addressing patient or population unmet needs and drive value areas historically underserved by the pharmaceutical industry. This includes new indications, patient sub-groups, areas of unmet need, small patient pools, and new therapies which dramatically increase the standard of care.</p> <p>The layer that reveals those who lead or fail to support and invest in global health and therapeutic areas where need is unmet.</p>	<p>Products with regulated technological innovations augmenting scientific and patient value independently or with a traditional medicine. This includes new health technologies, devices, diagnostics, biomarkers, apps, analytic tools, genomics, and companion devices.</p> <p>The element of technology convergence designed to expand definition and process of therapeutic innovation and approval.</p>

SOURCE: Accenture Research

**Exhibit 2
Prescription Pharmaceutical Sales Showing Contributions Of New Patient Science And New Treatment Science**



Source: Analysis By Accenture Research

\$127bn in 2018) but the fastest growth in New Treatment Science is seen when it is combined with New Patient Science. All forms of New Treatment Science made up 43% of revenue in 2018 and are projected to reach 48% of revenue in 2022, making this a very valuable dimension of science in total.

Although all of the sections analysed here increase in value over time, the fastest growing archetype for projected market share and projected value is the combined New Patient Science and New Treatment Science. The size of the effect of New Science on current and projected prescription pharmaceutical revenues suggests that valuable insight can be gained by breaking each dimension down

into its constituent archetypes.

Each Dimension of New Science can be described using various different archetypes and can be analysed in different ways, and at different points in the value chain. Archetypes may include drug combinations. This section describes the different archetypes of New Science, and their application.

New Treatment Science: Benefits From New Methods Of Managing Diseases

New therapeutic targets are a common aspect of New Treatment Science, and much of the traditional methodologies of driving growth in the pharma industry can be attributed to R&D in this area.

New mechanisms of action are a closely related and a frequent source of New Science, but requiring a more innovative approach than new targets, for example the use of Exon skipping through novel platform RNA splicing to treat Duchenne muscular dystrophy.

At a higher level, but much less frequently, new therapeutic classes can drive New Science, with RNAi drugs as a prominent example. Another frequent source of New Science is innovation around new formulations which drive improvements into patient care. For our analyses, reformulations that do not drive patient outcomes are not considered new.

New Treatment Science is changing the industry beyond creating more therapies. With the rise of cell and gene therapies, there has been a rise in companies serving those markets, including biotech companies with active R&D programs as well as technology companies working to improve research tools and methods.

New Patient Science: Innovations To Develop And Commercialize Treatments In Underserved Populations

The traditional angle of addressing new patient populations is to move into new indications. Although this remains a substantial revenue generating archetype, revenues for this archetype are slowly becoming a smaller proportion of the total prescription pharma market. Exhibit 4 illustrates this, with first-to-indication drug revenues, a historically important growth area, being roughly stable from \$77bn in 2012 to \$76.6bn in 2018 and a

**Exhibit 3
The Different Archetypes Of New Science**

NEW TREATMENT SCIENCE	NEW PATIENT SCIENCE	NEW TECH SCIENCE
Novel Classes & Modalities: (Cell, Gene Therapy, RNAi Biology)	Discrete Populations	Digital Medicines & Therapeutics
New Biologics	High Impact SoC	Companion Dx
Advanced Small Molecules	Clear Unmet Need	Evidence Technology – RWE
New Formulations W/Outcome	Under-Invested Diseases	Regulated SaMds & Applications
New Targets	Insufficient Supply	Regulated Health Technology
	New Indications	Developmental Biomarkers

SOURCE: Accenture Research

projected \$74.3bn in 2022, but with a decreasing percentage of the total pharma market: from 13% in 2012 to 11% in 2018 and a projected 8% in 2022.

In the context of the number of untreated indications decreasing over time, and a commercial focus on treating the more profitable indications leading to less profitable indications remaining, this suggests two things:

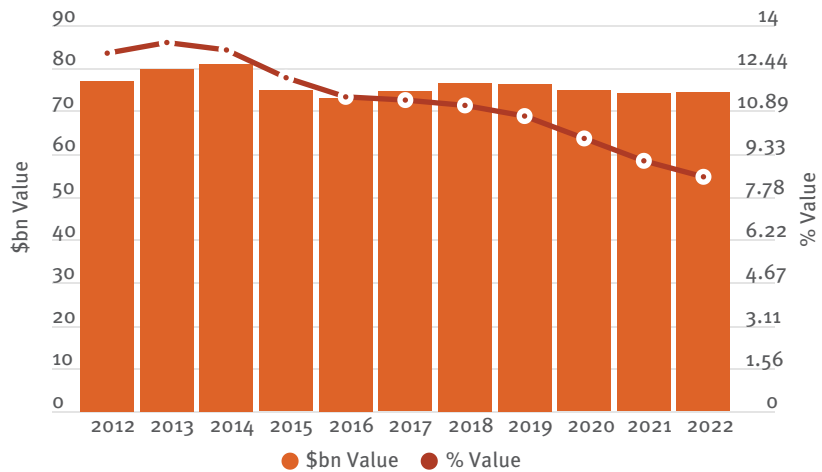
- First, focusing on new indications and untreated populations still maintains value for those who choose to continue R&D in these areas.
- Second, it will be increasingly difficult to grow market share; stagnation is likely if investors don't pivot into a new scalable growth strategy.

Although the core focus of trying to treat the untreated indications will maintain revenues for a while, failure to think long-term and make investments into research and development or strategic acquisitions to drive new areas of New Science now, could lead to eventual decline, irrelevance, and business failure.

One area of New Patient Science is focusing on areas of unmet need, or where drugs can have a large impact on the standard of care. The needs of patients for expedited approvals for serious conditions, or drugs which potentially have a large impact on the standard of care has been recognized by the FDA, which since 2012 can assign breakthrough therapy designation to development programs. Since inception of the classification, approved breakthrough therapies have rapidly gained share in volume and value, and by 2022 breakthrough designated therapies are forecast to make up 15% of total prescription pharma revenues.

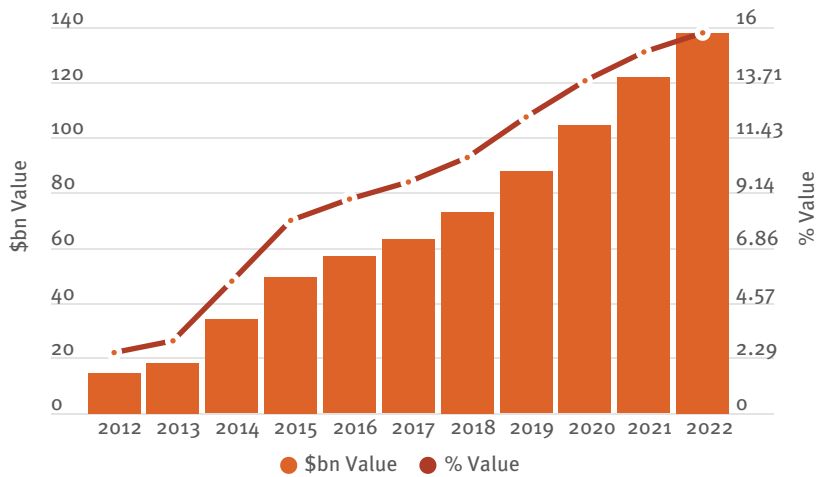
It can be expected that the effect of a new regulatory process increases from inception, but what is quite telling is the continuous increase in value and proportion of sales, neither of which show signs of slowing. This indicates that breakthrough designated therapies could become a major source of revenue for the pharmaceutical industry even more so than they are now, and therefore that investment into areas with high unmet need will continue to be lucrative.

Exhibit 4
Prescription Pharma Sales For Products First In Their Indication



SOURCE: Analysis By Accenture Research

Exhibit 5
Prescription Pharma Sales For Products With Breakthrough Therapy Designation



SOURCE: Analysis By Accenture Research

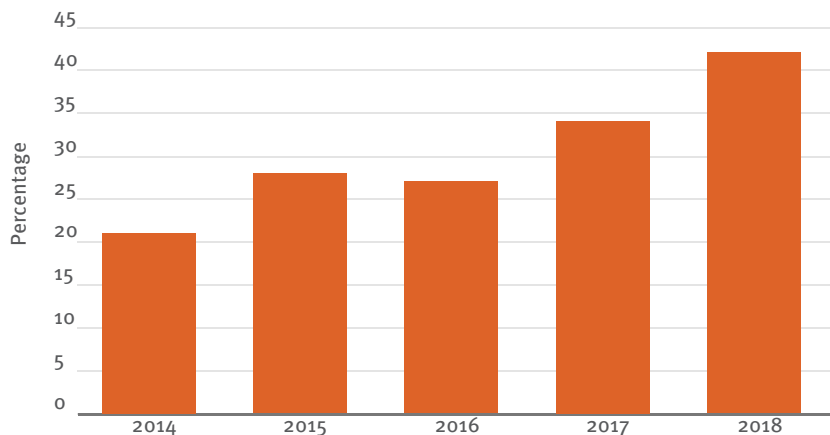
Similarly, areas with low number of patients, such as rare diseases, are another growth area for New Science. Orphan designated diseases are in increasing part of the pharmaceutical industry, currently providing 18% of revenue, and estimated to rise to 22% by 2022.

Another area of new patient science is looking into opportunities presented by populations with high unmet need due to the levels of income, or area specific diseases. According to a May 2019 10-year analysis by the Access to Medicine Foundation, people living in low- and middle-income countries (83% of world

population, but only 25% of projected 2020 pharma spend) may struggle with access to medicine. An estimated two billion people currently have no proper access to medicine. The same report discusses the trends in some pharma companies into R&D to tackle these issues, including neglected tropical diseases. In an increasingly competitive environment, with increasing societal pressures, this new area of interest could become an important investment to protect revenues.

Other areas of New Patient Science not explored here include areas of high unmet need in patient subgroups, or

**Exhibit 6
Proportion Of FDA Approvals For Personalized Medicines**



SOURCE: Personalized Medicine Coalition Report (PMC) 2018

in different lines of therapy, or where the drug supply is insufficient for the patient populations, with the notable exception of manufacturing related supply shortages.

Of course, New Patient Science has implications largely for the patients, but also drives investment into companies attempting to tackle orphan or rare diseases, many of which are genetic, as well as anti-infectives and vaccines. Added benefits from New Patient Science include improving patient visibility in an environment where the patient voice is increasingly important, as well as improving public perception of the pharmaceutical industry in an environment subject to increasing societal and regulatory scrutiny.

New Technological Science: Using Technology To Improve Outcomes Or Drive Drug Discovery

These technological innovations are an emerging dimension, driving patient value in improving treatment, care and access. As a relatively new area, the impact is more difficult to measure, however we expect the opportunity to be very large.

The biopharmaceutical industry is slowly moving from a one-size-fits-all approach to one where treatments are personalized to each patient. This is considered an area where substantial improvements can be made in treatment

outcomes, and regulatory authorities have recognized these by committing to accelerating personalized medicines. Significantly, 42% of medicines approved by the FDA in 2018 received this designation (see Exhibit 6). Personalized medicines include innovations such as using unique biomarkers or personalized molecular targets.

Digital interventions targeted at improving patient access and experience is another area of New Tech Science. The first wave of tech-based interventions in medicine were focused around home monitoring and diagnostics, but now we see an increase in tech-based innovations to improve patient access and patient adherence, often designed to work closely with the treatment regimen. In practice, this can be seen with Abilify MyCite, an oral pill that is embedded with sensors to track patient adherence, and with disease management systems such as WellDoc, which helps patients manage their diabetes and interfaces with health care professionals. Other innovations include companion diagnostics, and point-of-care tests.

Wearable technologies are another rapidly growing sub-archetype of New Tech Science. Innovations such as Quell, an FDA-cleared device, have shown to be effective at helping to alleviate symptoms of patients suffering from chronic pain.

The digital interventions archetype of New Tech Science is a relatively nascent

area of growth but shows rapid growth prospects with increased venture and private investments into the space. According to CBInsights, in 2018 alone, health technology received \$7.9bn in venture investments.

New Tech Science extends further than just new digital and new devices. Other technological innovations are included, such as new analytics and new evidence, including the use of real-world evidence (RWE). RWE is an area of great interest and has been successfully used in improving clinical studies and pharmacovigilance. Its applications will eventually extend to improving efficacy of drug discovery and reducing timelines. The use of analytics extends into genomics and can be applied to drug development. Early movements here include the partnership between 23&Me and GlaxoSmithKline PLC.

New Tech Science has implications for both patient outcomes, pharmaceutical revenues and for the discovery of new therapies. Already increased adherence can be seen with products like AdhereTech’s smart pill bottle, which in partnership with Diplomat Pharmacy has shown a 12% increase in patient retention, an increase in the number of refills per patient, and a decrease in the number of days without treatment. Investment into analytics can be seen in the Bristol-Myers Squibb Co. and Concerto partnership to use eurekaHealth, Concerto’s AI and machine learning platform.

New Tech Science has many implications for the industry, which is creating more and deeper partnerships to take advantage of this new area. Products such as companion diagnostics also require joint regulatory approval. Digital medicines also allow different types of companies to develop and operate in the industry, reducing barriers to entry.

Leaders In New Science Are Decisive About Investments

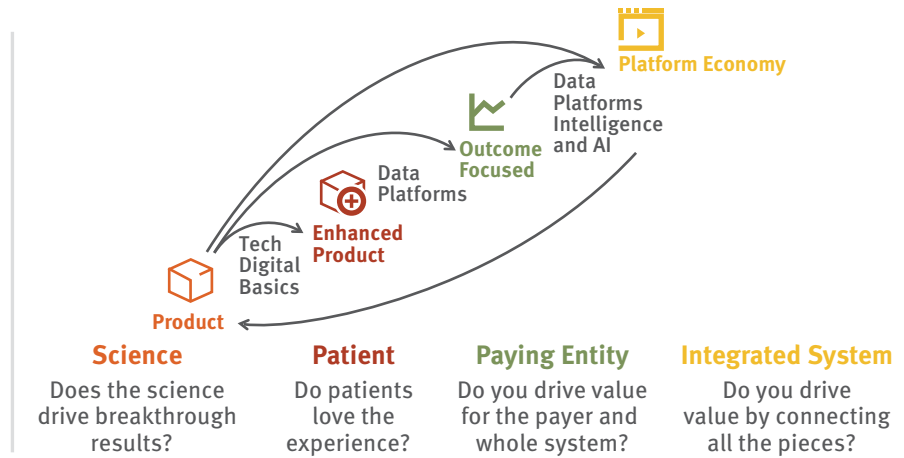
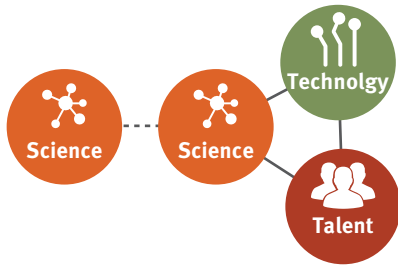
New Science: Biopharma’s New Growth Machine outlines the current leaders in New Science which are investing heavily into digital, data and genomics, and the biotech companies which generate a sizable portion of New Science.

For the immediate future, these leaders are increasing investment, partnerships

Exhibit 7 Seeing The Shift In Operations

NEW MODELS

Serving the patient, in a world where science has new reliance on **technology** – means a shift in how we operate



SOURCE: Accenture Research

and acquisitions into the existing areas of New Science. Over the long-term, real leadership may require a more proactive approach involving integrated New Science development platforms linked to advanced predictive analytics and intelligent solutions software.

Integrating New Science development approaches will involve moving expertise which is currently external in-house. Partnerships with external companies work well for short-term solutions, or to take advantage of low-hanging opportunities, but many such external providers do not have access to knowledge and expertise unique to the life sciences sector. Innovations coming from the external side often focus on simple concepts or reinforce a small angle of expertise of the founders, applied through existing infrastructure. To lead in the future, expertise in digital needs to be embedded in the organization to take advantage of valuable opportunities. In other words, biopharma companies need to start treating digital R&D similarly to that of their drug R&D, chiefly by accepting the risk profile required for new ideas to be tested.

Intelligent solutions provide further opportunities to lead in the future. Many products are logic-led, starting with what we know and investigating that for tracking or predictive capabilities, potentially then with intelligent solutions. This is great for taking advantage of what is already known, however that uses a fraction of the information available in

what is a data-rich environment. Future leaders should look to use what we do not know and have data lead New Science. Intelligent platforms with integrated data sources, could identify opportunities, in prediction and evidence to discover relationships between variables which may otherwise not be obvious. This would allow for more innovative design of New Science products. Pharma companies have been looking at this for a while with therapies, but data leading New Tech Science, or data leading New Patient Science, are proving to be valuable.

The current discussion on US pharmaceutical pricing also has a number of potential effects on the winners from New Science. Personalized medicine is unlikely to have a lower price threshold than many alternatives. In fact, New Patient Science is unlikely to be low cost where patient pools are small. Thus, the conclusion is that not only is New Science fueling the debate on pricing, it is also impacting investment decisions, with potential effects on the patient interest in keeping the progress around innovation alive.

In conclusion, our analysis of launched products has demonstrated that a large proportion of recent pharmaceutical market revenues have originated from New Science. Each dimension is a growing part of the pharmaceutical industry, with different growth characteristics. Although New Treatment Science contains many traditional directions for

innovation the greater potential of this dimension can be realized when combined with New Patient Science, which itself is an area of increasing potential. New Tech Science is an emerging area of increasing interest to the industry and has already been able to demonstrate improved patient outcomes, even in these early stages.

All told, New Science in each dimension is a driver for growth and opportunity in an increasingly complex biopharma industry. This is driving improvements in patient outcomes, the ability to address unmet need in different populations, and is driving the formation of start-up enterprises as well as acquisition of companies innovating in New Science.

The fact is the New Science dimensions and archetypes will allow the C-suite to obtain a fuller understanding of the present and future states of their company and the wider industry that surrounds it. This analysis observes company's moving across simpler product models to more advanced models. At the foundation, the determination of where they land is the combination of New Science in their portfolio. ❁

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On the Move

Recent executive appointments
in the life sciences industry



■ JEFFREY ECSEDY



■ JAN GROEN



■ WILLIAM GROSSMAN



■ THEODORA HAROLD

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Anil Singhal	Adicet Bio	Chief Executive Officer, President and Director	Canaan Partners	Executive in Residence	6-May-19
Dell Faulkingham	Akebia Therapeutics Inc	Chief Commercial Officer and Senior Vice President	Biogen Inc	Senior Vice President, Head, US MS Franchise	9-May-19
Steven Burke	Akebia Therapeutics Inc	Chief Medical Officer and Senior Vice President	Proteon Therapeutics Inc	Chief Medical Officer and Senior Vice President	17-Jun-19
Bill White	Akero Therapeutics	Chief Financial Officer and Head, Corporate Development	Deutsche Bank	Managing Director, Head, US Life Sciences Investment Banking	1-May-19
Mark Levick	Alvotech Iceland	Chief Executive Officer	Sandoz	Head, Development, Biopharmaceuticals	9-May-19
Juan-Jose Gonzalez	Ambu AS	Chief Executive Officer and President	DePuy Synthes	President	10-May-19
William Grossman	Arcus Biosciences	Chief Medical Officer	Bellicum Pharmaceuticals	Chief Medical Officer	2-May-19
Shaun Blakeman	Cantel Medical Corp	Chief Financial Officer and Senior Vice President	Medtronic	Senior Finance Director	13-May-19
Bill Huffnagle	CDx Diagnostics	Chief Executive Officer	Stryker	President, Joint Replacement	7-May-19
Greg Ryslik	Celsius Therapeutics	Chief Data Officer	Mindstrong Health	Vice President, Data Science	22-May-19
Michael Boretti	Celsius Therapeutics	Chief Business Officer	Epizyme	Vice President, Business Development	22-May-19
Carl O'Connell	Cerebrotech Medical Systems	Chief Executive Officer	Xtant Medical Technologies	President and Chief Executive Officer	8-May-19

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ONLINE**

Take an interactive look at recent executive-level company changes and promotions in the biopharma, medical device and diagnostics industries.

Visit: invivo.pharmaintelligence.informa.com



■ **BILL HUFFNAGLE**



■ **LLOYD KLICKSTEIN**



■ **DERRICK SUNG**



■ **BILL WHITE**

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Steven Engle	CohBar Inc	Chief Executive Officer	Averigon Consulting	Chief Executive Officer	15-May-19
Cord Friedrich Stahler	Dentsply Sirona	Chief Technology Officer	Merck KGaA	Senior Vice President, Head, Global Medical Device and Service Business	1-May-19
Nevena Zubcevik	Endonovo Therapeutics	Chief Medical Officer	Harvard Medical School/Partners Healthcare	Attending Physician	1-Jul-19
Gino Van Heeke	Engitix	Chief Scientific Officer	Ablynx	Senior Director, Discovery and Early Development	7-May-19
Chockalingam Palaniappan (Palani)	Epic Sciences	Chief Technology Officer	Terumo BCT	Executive Vice President, Innovation and Development	22-May-19
Franco Fontana	Esaote SpA	Chief Executive Officer and Director	Ebit AET	Director, Business Unit	13-May-19
Carsten Thiel	EUSA Pharma (UK) Ltd	President, Europe	Abeona Therapeutics	Chief Executive Officer	15-May-19
Darrel P. Cohen	EUSA Pharma (UK) Ltd	Head, Clinical Development	Pfizer Oncology	Vice President, Clinical Development Leader	15-May-19
Wende Chen	Everest Medicines	Chief Commercial Officer	Roche Pharma China	Vice President, Corporate Affairs, Market Access and Channel Management	10-May-19
Howard Stern	FogPharma	Chief Scientific Officer	Juno Therapeutics	Vice President, Translational Sciences	6-May-19
Magnus Christensen	Medivir AB	Chief Financial Officer	O'Learys Trademark	Chief Financial Officer	12-Aug-19
Stephanie Muir	Midmark Corp	Chief Technology Officer	Johnson & Johnson	Vice President, Digital Surgery	1-Aug-19

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Jan Groen	Novigenix SA	Chief Executive Officer and Director	MDxHealth SA	President and Chief Executive Officer	13-May-19
Christopher R. Heery	Precision BioSciences Inc	Chief Medical Officer	Bavarian Nordic	Chief Medical Officer	14-May-19
Matthew Swiggum	PROTEOR Group	Chief Executive Officer and President, PROTEOR USA	Amputee Coalition of America	Regional President and Chief Executive Officer	9-May-19
Derrick Sung	Pulmonx Corp	Chief Financial Officer	iRhythm Technologies	Executive Vice President, Strategy and Corporate Development	9-May-19
Maria Koehler	Repare Therapeutics	Chief Medical Officer and Executive Vice President	Bicycle Therapeutics	Chief Medical Officer	1-May-19
Lloyd Klickstein	restORbio Inc	Chief Scientific Officer	Novartis Institutes for Biomedical Research	Global Head, Translational Medicine, New Indication Discovery and Exploratory Disease	14-May-19
Robin G. Taylor	Seattle Genetics	Chief Commercial Officer	AstraZeneca	Vice President, Immuno-Oncology Franchise Head, Oncology Business Unit	21-May-19

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
Daniel Barber	Aquestive Therapeutics	Chief Operating Officer and Senior Vice President	Senior Vice President, Chief Strategy and Development Officer	6-May-19
Joanne Smith-Farrell	bluebird bio	Chief Business Officer	Senior Vice President, Corporate Development and Strategy	1-May-19
Peter G. Clifford	Cantel Medical Corp	Chief Operating Officer and Executive Vice President	Chief Financial Officer, Executive Vice President and Member of Office of the Chairman	13-May-19
Theodora Harold	Crescendo Biologics Ltd	Chief Executive Officer	Chief Financial Officer and Chief Business Officer	1-May-19
Eugenio Biglieri	Esaote SpA	Chief Operating Officer and Director	Director, Global Service	13-May-19
R. Scott Areglado	iCAD Inc	Chief Financial Officer	Interim Chief Financial Officer, Vice President and Corporate Controller	1-May-19
Andre Godin	IntelGenx Corp	President and Chief Financial Officer	Chief Financial Officer	8-May-19
Misty Stevens	InterveXion Therapeutics	Chief Operating Officer	Operations Director	13-May-19
Jason Sager	Kyn Therapeutics	Chief Medical Officer	Interim Chief Medical Officer	7-May-19
Jeffrey Ecsedy	Kyn Therapeutics	Chief Scientific Officer	Senior Vice President, Research and Development	7-May-19
Omar Khwaja	Voyager Therapeutics	Chief Medical Officer and Head, R&D	Chief Medical Officer	28-Jun-19
Jason Asper	Wright Medical Group NV	Chief Digital Officer and Senior Vice President	Senior Vice President, Strategy and Corporate Development	7-May-19

DIRECTORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Patrick Machado	Adverum Biotechnologies	Chairman	2-May-19
Burke W. Whitman	Amicus Therapeutics Inc	Director	13-May-19
Andrew Marshall	Ascendis Health	Chairman	6-May-19
Jeffrey Kraws	Avivagen Inc	Chairman	14-May-19
John T. Kilcoyne	Cerebrotech Medical Systems	Director	8-May-19
Sue Paish	Contextual Genomics Inc	Chairman	1-May-19
Wu Guangming	Esaote SpA	Chairman	13-May-19
Gregory Moore	Hill-Rom Holdings Inc	Director	7-May-19
Nicole Seligman	MeiraGTx	Director	10-May-19
Maurizio PetitBon	NOXXON Pharma AG	Chairman	3-May-19
Charles Chon	Pulmonx Corp	Director	9-May-19
Carol Schafer	Repare Therapeutics	Independent Director	1-May-19
Akshay Vaishnav	Scholar Rock	Director	21-May-19
Charles W. Federico	Titan Medical Inc	Chairman	1-May-19

ADVISORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Robert Petit	Advaxis Inc	Chairman, Scientific Advisory Board	3-Jun-19
Malcolm K. Brenner	Allogene Therapeutics	Scientific Advisory Board Member	1-May-19
Robert Abraham	Allogene Therapeutics	Scientific Advisory Board Member	1-May-19
Stephen J. Forman	Allogene Therapeutics	Scientific Advisory Board Member	1-May-19
Wendell Lim	Allogene Therapeutics	Scientific Advisory Board Member	1-May-19
Robert Coleman	Scancell Ltd	Chairman, Clinical Advisory Board	10-May-19
Stephen Chan	Scancell Ltd	Clinical Advisory Board Member	10-May-19
Guenther Koehne	Xenetic Biosciences Inc	Scientific Advisory Board Member	2-May-19

RESIGNATIONS/RETIREMENTS

EXECUTIVE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE	MOVE TYPE
David Apelian	Eiger BioPharmaceuticals Inc	Chief Operating Officer and Executive Medical Officer	14-Jun-19	Resignation
Khalid Ishaque	Pixium Vision	Chief Executive Officer and Director	13-May-19	Resignation
Torben Straight Nissen	Rubius Therapeutics Inc	President	1-Jul-19	Resignation
Edward Conner	Sangamo Therapeutics Inc	Chief Medical Officer and Senior Vice President	31-May-19	Resignation
Dinah Sah	Voyager Therapeutics	Chief Scientific Officer	28-Jun-19	Retirement

Deal-Making

Covering deals made May 2019

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

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

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

IN VITRO DIAGNOSTICS

FINANCINGS

Public offering nets \$304.7m for **Guardant Health**

Public offering nets \$138m for **Veracyte**

MEDICAL DEVICES

MERGERS & ACQUISITIONS

3M to buy **Acelity**; enterprise value \$6.7bn

Boston Scientific to pay \$465m up front for **Vertiflex**

Medtronic pays undisclosed sum for **Titan Spine**

Misonix buys **Solys Medical** for \$97m plus net debt

Perrigo buys **Ranir Global** for \$750m cash

CyberHeart scooped up by **Varian Medical Systems**

Wishbone Medical buys **CSpine**

ALLIANCES

Cook Medical to sell **Ambu's** single-use duodenoscopes in the US following FDA approval

Takeda divests **TachoSil** to **Ethicon**

Vericel gets North American rights to **MediWound's NexoBrid**

Novartis to co-promote **Tilak's OdySight** medical videogame in France

FINANCINGS

Neovasc grosses \$11.5m through debt and share offerings

Second IPO attempt successful for **TransMedics**; nets \$97.4m

PHARMACEUTICALS

MERGERS & ACQUISITIONS

Amgen offers to pay \$166.9m for **Nuevolution**

Recapitalized **Aegerion** scooped up by **Amryt**

BioNTech buys up **MabVax's** antibody assets

Evotec acquires biologics manufacturer **Just** for up to \$90m

H. Lundbeck acquires **Abide** for up to \$400m

Merck acquires **Peloton** for up to \$2.2bn

Therachon scooped up by **Pfizer**

ALLIANCES

Adaptimmune and **Alpine Immune Sciences** enter cell therapy deal

AZ's Acerta Pharma and **Forty Seven** enter lymphoma trial collaboration

Transgene and **AstraZeneca** develop oncolytic immunotherapies

BI, Gubra announce second collaboration within the obesity field

Lilly licenses non-opioid pain candidate from **Centrexion**; PDV near \$1bn

Chiesi gets rights to **Santhera's** ophthalmic drug **Raxone**

Roche partners aldosterone synthase inhibitor with start-up **CinCor Pharma**

CStone and **Numab** pen immuno-oncology deal

Cumulus licenses preclinical cancer candidate from **Ligand**

Curadev licenses STING agonist to **Takeda**

Exelixis options rights to **Iconic's** ADC project **ICON2**

Goldfinch signs major partnership with **Gilead**

Glenmark to co-promote **Otonomy's** **Otiprio** in the US

HanX to develop and sell rigosertib in China for **Onconova**

Iconic Therapeutics to use **Zymeworks' ZymeLink** ADC platform

Spectrum gets rights to **ImmunGene's** IO platform and related assets

Hansoh Pharma licenses rights to **Viela's** autoimmune disease candidate inebilizumab

Kymera, Vertex team up in protein degradation

Novartis pays up to \$5.3bn to acquire **Takeda's Xiidra** for dry eye

Takeda launches **Phathom**; grants vonoprazan license

Parvus signs second Big Pharma deal, this time with **Genentech**

Takeda licenses **SkySTAR** candidates for neurodegenerative diseases from **Skyhawk**

FINANCINGS

ADMA Biologics nets \$48.6m via FOPO

Amicus nets \$164.5m via public offering

Aptose nets \$17.2m via public offering

Armata raises \$10m via financing concurrent with closing of **Amplphi/C3J** merger

Athenex brings in \$100m through PIPE

Axcella Health nets \$66.4m via IPO

Bicycle Therapeutics nets \$56.9m through US IPO

BridgeBio seeks to go public

Registered direct offering nets \$5.64m for **Can-Fite**

Clovis Oncology enters \$175m financing agreement to help pay for **Rubraca** combo trials

Cortexyme nets \$80.2m in Nasdaq IPO

Public offering nets \$29.7m for **Mustang Bio**

Galectin closes rights offering, raises \$44.5m

Gossamer enters \$150m debt facility with MidCap; gets \$30m up front

Initial public offering nets \$46.5m for **IDEAYA Biosciences**

Insmed nets \$236.3m via FOPO

Intercept grosses \$10m through PIPE
Public offerings net \$383.4m for

Intercept Pharmaceuticals

Magenta Therapeutics nets \$60.9m via public offering

Mersana enters \$20m loan facility with SVB; gets \$5m up front

Milestone Pharma goes public netting \$76.7m

NextCure's IPO nets \$80.2m

Novan sells royalty rights to molluscum candidate SB206 to **Ligand** for \$12m

Public offering nets \$10.3m for **Oncosec**

Regulus gets \$16.2m in first PIPE tranche; could receive another \$25.1m

Myovant nets \$117.5m through public offering

Translate Bio grosses \$47.5m via PIPE

Trevi Therapeutics nets \$14m in PIPE concurrent with IPO

Trevi Therapeutics nets \$51.2m through Nasdaq IPO

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

FINANCINGS

Twist Bio nets \$85.1m via FOPO

IN VITRO DIAGNOSTICS

FINANCINGS

GUARDANT HEALTH INC.

Precision oncology firm **Guardant Health Inc.** netted \$304.7m through the public offering of 4.5 million common shares at \$71. The company markets two liquid biopsy products--*Guardant360* and *GuardantOMNI*--which are used in treatment selection and drug development settings, respectively, and is also developing assays for cancer recurrence detection and early disease screening. (May)

Investment Banks/Advisors: Bank of America Merrill Lynch; Cowen & Co. LLC; JP Morgan Chase & Co.; William Blair & Co.

VERACYTE INC.

Veracyte Inc. (genomic testing) netted \$138m through a public offering of 6.3 million common shares (including the over-allotment) at \$23.25. The company will use some of the proceeds to repay \$12.4m on an outstanding loan and will put the rest of the funds towards corporate needs, including potential strategic investments or acquisitions. (May)

Investment Banks/Advisors: BTIG LLC; Janney Montgomery Scott Inc.; Morgan Stanley & Co.; SVB Leerink; William Blair & Co.

MEDICAL DEVICES

MERGERS & ACQUISITIONS

3M CO.

ACELITY LP INC.

3M & Co. will acquire wound care firm **Acelity LP** and its **KCI** subsidiaries from an investor consortium led by Apax partners for a total enterprise value of \$6.7bn (\$4.4bn cash plus assumption of net debt). (May)

Acelity's history dates back to the 1970s and the formation of **Kinetic Concepts Inc.** (KCI), a company well known for its rehabilitation products and eventually as designer of the first negative pressure wound therapy (NPWT) systems and the V.A.C. brand. KCI acquired regenerative medicine firm LifeCell in 2008, and in 2011 was taken private through a \$6.3bn buy-out by funds advised by Apax Partners, affiliates of the Canada Pension Plan Investment Board (CPPIB), and the Public

Sector Pension Investment Board (PSP) (who are all still owners). Come 2013, KCI bought wound healing firm Systagenix, and it was after this transaction that KCI's owners decided to operate KCI, LifeCell, and Systagenix under one brand, called Acelity. (LifeCell has since been divested to **Allergan** through a \$2.9bn deal in 2016). Through the current acquisition, 3M will operate Acelity and its subsidiaries under the company's **3M Medical Solutions** business, which offers products including advanced and acute wound care dressings and products, medical tapes, sterilization products, and patient warming systems. Acelity's 2018 revenues came in at \$1.47bn, with reported EBITDA of \$441m. The company's brands include the V.A.C. NPWT system and associated products, *Abthera* open abdomen negative pressure therapy, *Tielle Licalock* adhesive dressings, *Promogran* protease modulating matrix, and a variety of additional dressing and wound care products. Two weeks prior to the acquisition announcement, Acelity was in line for an initial public offering through the creation of **KCI Holdings Inc.**, a holding company for all of Acelity's brands that filed an S-1 and was rumored to be expecting up to \$500m if the IPO had gone final. Apax, CPPIB, and PSP will now see an even larger exit through the purchase by 3M. (The acquisition is the largest ever for 3M.) Investment Banks/Advisors: Credit Suisse Group (3M Co.)

BOSTON SCIENTIFIC CORP. VERTIFLEX INC.

Boston Scientific Corp. is acquiring closely held device maker **Vertiflex Inc.** for \$465m in cash up front. Boston Scientific could also shell out additional money in the form of commercial milestones over the next three years. (May)

Fourteen-year-old Vertiflex sells the FDA-approved *Superion* indirect decompression system designed to improve mobility and reduce pain in patients with lumbar spinal stenosis (LSS). Via a minimally invasive procedure, the system is implanted to create space between the spinous processes of the vertebrae, thus reducing pressure on the nerves and helping to relieve pain, numbness, and cramping in the legs. This procedure is an option for patients who have not responded positively to first-line therapies--including oral pain medication

and steroid injections--but whose symptoms aren't severe enough to warrant spinal fusion or laminectomy. In November 2018, Vertiflex published results from a randomized controlled trial of *Superion* suggesting that, in light of the current opiate epidemic, the system offers an effective option to opioid therapy. Conducted under an IDE, the study showed an 85% decrease in the number of patients using opioids five years after being treated with *Superion* interspinous process decompression device. The acquisitions allows Boston Scientific to expand on its pain management offerings such spinal cord stimulation and radiofrequency ablation.

MEDTRONIC PLC TITAN SPINE LLC

Medtronic PLC is acquiring closely held device maker **Titan Spine LLC** for an undisclosed sum. (May)

Titan Spine offers a full line of *Endoskeleton* titanium interbody implants that incorporate its *nanoLOCK* technology--the only FDA-cleared nanotechnology for the spine--to promote bone growth following vertebral fusion surgery. The devices have been shown to promote a significantly greater amount of bone growth factors necessary for fusion when compared to other commonly used interbody fusion device materials such as polyetheretherketone (PEEK) and smooth titanium. Interbody implants (spaces) are inserted between the vertebrae to relieve pressure on nerves and hold the vertebrae in place during surgical fusion. Titan's devices are complementary to Medtronic's own products for spine and orthopedic surgery, including biologics to promote post-surgery bone growth.

MISONIX INC. SOLYS MEDICAL LLC

Misonix Inc. penned a definitive agreement to acquire privately held regenerative medicine firm **Solys Medical LLC** in an all-stock transaction. Misonix will issue approximately 5.7 million new shares valued at \$97m, and will also assume \$20m in outstanding secured debt. (May)

Solys was founded as Soluble Systems in 2017 and markets the *TheraSkin* living human split-thickness extracellular matrix, a skin allograft containing 16 cytokines and 14 types of collagen to promote healing in difficult-to-treat wounds. It is estimated that *TheraSkin* will bring in \$32m in sales during 2019. Misonix notes that the product is highly complementary to its own *SonicOne* ultrasonic wound debridement system. Misonix shareholders will own 64% of the combined entity post-acquisition. Pro-forma sales are expected to total over \$80m. Investment Banks/Advisors: JP Morgan Chase & Co. (Misonix Inc.); Canaccord Genuity Inc. (Solys Medical LLC)

PERRIGO CO. PLC RANIR GLOBAL HOLDINGS LLC

Perrigo Co. PLC penned a definitive agreement acquire **Ranir Global Holdings LLC**, the largest private label oral care company in the world for \$750m cash (\$685m including cash tax benefits). (May)

Ranir's portfolio holds over 300 products--including power toothbrushes and heads, whitening strips, manual toothbrushes, floss, dentures and travel kits--that it markets to retailers and distributors in more than 50 countries for sale under private label/store brand names; 2018 sales came in at about \$287m. The company also sells the *Rembrandt* toothpaste line and *Placks* brand of floss. Perrigo enhances its over-the-counter offerings in the self-care market through the acquisition. The company's personal care business holds topical treatments and intimate care products in the dermatology, first aid, hair, feminine hygiene, and men's and sexual health areas. It also sells private label products for cough-cold, pain, smoking cessation and GI issues. (Additionally, Perrigo had an animal health business, but just prior to announcing the Ranir acquisition, the company revealed that it would sell that unit to PetIQ for \$185m.) The animal health and Ranir transactions help Perrigo step firmly on its path towards a "full consumer self-care transformation," helping the company move from a health care to self-care focus and hopefully turn around its recent earnings slump. The deal should be immediately accretive to Perrigo's net sales growth, adjusted operating income growth, and adjusted earnings per share. Investment Banks/Advisors: William Blair & Co. (Ranir Global Holdings LLC)

VARIAN MEDICAL SYSTEMS INC. CYBERHEART INC.

Varian Medical Systems Inc. is acquiring private cardiovascular device maker **CyberHeart Inc.** for an undisclosed sum. (May)

CyberHeart has developed the first non-invasive treatment for cardiac arrhythmias. The company's intellectual property covers cardiac radioablation and other types of radiosurgery for cardiovascular disease. Early clinical trials have shown positive results in ventricular tachycardia. There are currently no FDA-approved cardiac radioablation technologies. Over the last few years Varian has been building its portfolio through acquisitions. Its most recent purchase was **humediQ Global** in August 2018 to boost its radiation therapy business.

WISHBONE MEDICAL INC. CSPINE INC.

WishBone Medical Inc. acquired fellow spine and orthopedic implants maker **CSpine Inc.** for an undisclosed amount. (May)

Until now, Wishbone had been focused

on pediatric orthopedics. With the CSpine purchase, the company enters the global spine market within pediatric orthopedics and has the opportunity to help children with deformities of the spine. Research suggests that nearly 30k adolescents in the US will undergo surgical treatment for scoliosis this year. CSpine's technologies can potentially produce devices more cost-effectively and faster than leading orthopedic device companies. WishBone and CSpine's executives have more than 100 years of combined expertise in medical device engineering, development, and manufacturing. Following the acquisition, CSpine's implants will be combined and sterile packed with single-use disposable instruments at Red Star Contract Manufacturing and be renamed **Red Star Medical Solutions**.

ALLIANCES

AMBU AS COOK GROUP INC.

Cook Medical Inc.

Ambu AS granted **Cook Medical Inc.** rights to distribute its single-use, disposable duodenoscope in the US. (May)

The product does not yet have FDA approval but Ambu anticipates approval sometime before the end of September 2020. Ambu's sterile duodenoscope is designed to prevent cross-contamination which is prevalent with reusable endoscopes used during gastroenterology procedures. Cook plans to bring the product to market for patients undergoing endoscopic retrograde cholangio-pancreatography (ERCP) procedures.

JOHNSON & JOHNSON *Ethicon Inc.*

TAKEDA PHARMACEUTICAL CO. LTD.

Takeda Pharmaceutical Co. Ltd. entered into an agreement to divest its *TachoSil* fibrin sealant patch and related assets to **Johnson & Johnson's Ethicon Inc.** for \$400m in cash. (May)

TachoSil is a surgical patch designed for quick and effective bleeding control. The FDA approved the BLA in 2015 for use as an adjunct to hemostasis in cardiovascular and hepatic surgeries. In FYE March 31, 2018, the product generated net sales of \$155m. Takeda will maintain ownership of *TachoSil*'s Austrian manufacturing facility and continue to manufacture and supply the product to Ethicon long term. Concurrent with the transaction, **Novartis** agreed to acquire Takeda's dry eye drug *Xiidra* (lifitegrast) 5% topical solution and associated assets to further boost its ophthalmic pharmaceuticals portfolio. That high-priced deal involved \$3.4bn upfront in cash and up to \$1.9bn in potential milestone payments to Takeda, which plans to use proceeds from both divestitures to reduce debt and accelerate deleveraging toward its target of 2.0x net debt/adjusted EBITDA in the medium term. The deals

allow Takeda to focus on core business areas (gastroenterology, rare diseases, plasma-derived therapies, oncology, and neuroscience) following its acquisition of **Shire**. Investment Banks/Advisors: Nomura Securities International Inc. (Takeda Pharmaceutical Co. Ltd.)

MEDIWOUND LTD. VERICEL CORP.

MediWound Ltd. granted **Vericel Corp.** exclusive rights to commercialize the topical burn treatment *NexoBrid* in North America. (May)

Vericel pays \$17.5m up front, \$7.5m upon US approval of the therapy, and up to \$125m in sales milestones, plus high-single digit to low-double digit royalties. MediWound will manufacture the product for a supply price of cost plus a fixed margin percentage. *NexoBrid* contains proteolytic enzymes enriched in bromelain (a protein extract from the stem of pineapples). The topically applied product removes eschar (dead or damaged tissue) from deep partial- and full-thickness burns in about four hours without damaging surrounding healthy tissue, and without the need for surgical excisions or autografts. It was approved by the EMA and other international bodies, and has orphan biologic designation in the US. (A BLA filing with the FDA is expected by the end of this year.) The US Biomedical Advanced Research and Development Authority (BARDA) awarded MediWound a \$132m contract for development, manufacturing, and procurement of *NexoBrid*; Vericel will hand over to MediWound a percentage of the gross profits on BARDA orders and double-digit royalties. Vericel joins a growing list of global *NexoBrid* commercialization partners, including **BexPharm** (South Korea), **Covaleo** (Mexico) **Avalon** (Colombia, Peru, Ecuador, Chile, and Panama), and **Kaken** (Japan). Investment Banks/Advisors: Moelis & Co. (MediWound Ltd.)

NOVARTIS AG TILAK HEALTHCARE

Novartis AG agreed to partner with digital health start-up **Tilak Healthcare** to exclusively co-promote to ophthalmologists in France the latter's *OdySight* prescribed therapeutic mobile videogame. (May)

Founded in 2016, Tilak has since developed an application targeting patients with chronic eye diseases, including those impacting the macula (the part of the retina responsible for high-acuity vision), such as age-related macular degeneration (AMD), diabetic retinopathy, and high myopia. Available as an app on a mobile device, *OdySight* is the company's first clinically validated mobile game in which the player performs visual tests and then completes a series of puzzles to evaluate both cognitive and visual abilities. *OdySight* monitors a patient's visual

parameters (predefined by a physician) by collecting data after game play, including vision loss detection, and securely transmitting it to both patient and physician to develop a personalized treatment plan and enable follow-up care. The deal supports Novartis' digital medicine strategy within ophthalmology, one of the Big Pharma's core therapeutic areas.

FINANCINGS

NEOVASC INC.

Neovasc Inc. (developer minimally invasive devices for transcatheter mitral valve replacement (*Tiara*) and refractory angina (*Neovasc Reducer*)) grossed \$11.5m through the sale of debt and common shares to Strul Medical Group. It sold Strul a 15% original issue discount convertible debenture for gross proceeds of \$9.8m. The debt matures in four years with interest of 8% for the first year and 10% for the following three years, with 3% of the total interest accruing each year and becoming payable at the end of the term. Strul can convert the debt at \$0.75 per common share for the first two years, \$0.85 for the third year, and \$0.97 for the final year. Neovasc also grossed \$1.7m through the sale of 3.45 million common shares at \$0.515 each to Strul. The proceeds will support R&D and commercial activities. (May)

PHARMACEUTICALS

MERGERS & ACQUISITIONS

AMGEN INC. NUEVOLUTION AS

Amgen Inc. is offering to pay \$166.9m (SEK1.61bn) (\$3.37 per share; a 170% premium based on the ten-day average) in cash for Danish firm **Nuevolution AB**. (May)

The companies are partners under an October 2016 agreement in which Nuevolution licensed Amgen an exclusive option to develop and commercialize small-molecule cancer and neuroscience therapies. To date, Amgen has optioned two cancer candidates. The acquisition combines both firm's strengths--Nuevolution in drug discovery expertise and Amgen's capabilities in R&D, manufacturing, and commercialization--and allows Amgen to serve patients across various therapy areas. Nuevolution's main revenue generator is its *Chemetics* drug discovery platform, which it has licensed to Big Pharmacos **Novartis**, **Boehringer Ingelheim**, **Merck**, and **Janssen**. *Chemetics* enables DNA-encoded synthesis of billions of chemically diverse drug-like small molecules and can rapidly and efficiently screen and optimize those compounds. Nuevolution went public in late 2015 raising \$29.4m. At that time the firm revealed plans to develop five to six small-molecule preclinical and clinical pro-

grams over a three-year period. It currently has programs in inflammation, cancer, and immuno-oncology. Nuevolution's pipeline is led by a small-molecule retinoic acid-related orphan nuclear receptor gamma T (ROR γ T) inhibitor for dermatology indications including psoriatic arthritis. The firm gained the candidate through a potential \$478.5m licensing agreement with **Almirall**. Nuevolution's investors include SEB Foretagsinvest, Sunstone Capital, SEB Venture Capital, SEB Utvecklingsstiftelse, Novo AS, Nordic Biotech, and the Danish Investment Fund. Investment Banks/Advisors: PJT Partners; Skandinaviska Enskilda Banken AB (Amgen Inc.)

AMRYT PHARMA PLC NOVELION THERAPEUTICS INC.

Aegerion Pharmaceuticals Inc.

Amryt Pharma PLC is buying **Novelion's Aegerion Pharmaceuticals Inc.**, which is recapitalizing through a court-supervised Chapter 11 process. (May)

Amryt is concurrently raising \$60m in equity funding for the deal. The merged entity will have combined pro forma 2018 revenues of \$136.5m, and will be re-admitted to the Euronext in Dublin and London's AIM market and have a dual listing on the Nasdaq. The recapitalization imputes an enterprise value to Aegerion and Amryt of \$395m and \$146m, respectively. The pre-money implied transaction equity valuations are Amryt \$120m and Aegerion \$190.7m. Amryt's executives will continue to lead the firm. The companies had already been partners through a late 2016 deal in which Amryt got exclusive rights to sell Aegerion's *Lojuxta* (lomitapide) capsules for homozygous familial hypercholesterolemia in the European Economic Area, Switzerland, Turkey, and certain Middle Eastern and North African countries including Israel. The product is sold as *Juxtapid* in the US, Canada, and some Latin American countries. Through the acquisition Amryt also gains Aegerion's *Myalept* (metreleptin) leptin hormone replacement therapy for generalized lipodystrophy. Aegerion paid **AstraZeneca** \$325m for the drug in 2014. Amryt plans to pursue additional indications for metreleptin and lomitapide. The therapies will join Phase III AP101 (oleogel-S10) for epidermolysis bullosa (EB), preclinical AP102 for acromegaly, and preclinical AP103 gene therapy for EB and other topical indications. As part of the acquisition agreement, Amryt shareholders could receive earn-outs in the form of contingent value rights worth up to \$85m based on development of AP101. Investment Banks/Advisors: Evercore Partners (Novelion Therapeutics Inc.)

BIONTECH AG MABVAX THERAPEUTICS HOLDINGS INC.

BioNTech SE scooped up antibody assets from bankrupt **MabVax Therapeutics Hold-**

ing Inc. (cancer drug developer). (May)

The deal comes about five months after MabVax announced that it engaged Objective Capital Partners as its advisor to seek out the potential sale of its pre-clinical and clinical assets. In March, the company filed for bankruptcy and named BioNTech (and two other undisclosed bidders) as potential buyers for some of the company's assets. (The bankruptcy document notes that BioNTech's offer was for \$3.7m, but the actual amount of the sale was not revealed.) BioNTech now takes on MabVax's lead candidate MVT5873 (IgG1 monoclonal antibody in Phase I for pancreatic cancer) in addition to pre-clinical antibody assets, infrastructure, and laboratory equipment, all of which will help BioNTech expand its own antibody portfolio and complement its *RiboMABS* development platform, which is used to generate mRNA-encoded antibody drug candidates. MabVax will reportedly retain some propriety preclinical assets and existing third-party service agreements.

EVOTEC SE JUST BIOTHERAPEUTICS INC.

Evotec SE agreed to acquire privately held **Just Biotherapeutics Inc.**, a US firm that develops technologies and services for the manufacture of biologics. (May)

Evotec will pay up to \$90m (\$60m in cash up front and up to \$30m in performance-based earn-outs over the next three years). Founded in 2014, Just offers machine-driven technologies that speed up development and reduce manufacturing and commercial costs of therapeutic proteins, including anti-HIV antibodies, by integrating molecular, process, drug, and manufacturing design steps. With funding from backers including the **Bill & Melinda Gates Foundation**, **Merck & Co. Inc.**, Lilly Asia Ventures, and Arch Venture Partners, the company has raised \$29m since its inception and recorded 2018 revenues of approximately \$22.3m. Technologies incorporated under Just's integrated *J.DESIGN* biologics' drug development platform include process development tool *J.MD*, which uses a machine learning-based computer-aided design interface to predict and select optimal molecules for further development; *JP3* lab and computational tools to enable rapid delivery of a high-throughput manufacturing process and a cGMP early clinical manufacturing facility; and *J.POD* for flexible and modular larger-scale manufacturing of both clinical- and commercial-stage biologics. The addition of Just gives Evotec a US presence, provides it with more efficient drug development and manufacturing capabilities and services, and enhances Evotec's existing small-molecule offerings, enabling it to grow its pipeline to include biologics in the cancer and

inflammation, and CNS, infectious, and metabolic disease areas.

H. LUNDBECK AS ABIDE THERAPEUTICS INC.

H. Lundbeck AS agreed to acquire privately held fellow CNS-focused **Abide Therapeutics Inc.** (endocannabinoid modulators). (May)

Lundbeck will pay \$250m in cash up front and a potential \$150m more in earn-outs contingent on the achievement of certain development and sales milestones. With the acquisition, the Danish pharma gains Abide's proteomic drug discovery platform focused on selective serine hydrolase inhibitors. The eight-year-old company's platform combines three components: a chemical library of 20k-plus compounds with activity against serine hydrolases (one of the largest and most diverse classes of enzymes with vital roles in many pathophysiological processes); metabolomic methodology enabling rapid understanding of the serine hydrolase substrates; and an activity-based protein profiling (ABPP) assay technology. Enhancing Lundbeck's already extensive current CNS development pipeline, it gains Abide's development candidates led by ABX1431 (an oral inhibitor of the endocannabinoid modulator monoacylglycerol lipase (MGLL), in Phase IIa for Tourette syndrome (with a 20% likelihood of approval in this indication, 3% above average) and Phase I for pain and levodopa-induced dyskinesia) and five other preclinical compounds. In addition, Lundbeck gets Abide's US-based laboratory, which will become a drug discovery hub for Lundbeck. Under a since-terminated 2014 deal, **Celgene** previously held ex-US rights to ABX1431 as well as an option to acquire Abide, but that agreement was replaced with a 2018 transaction giving Celgene worldwide rights to Abide's ABX1772, a preclinical MGLL inhibitor for an undisclosed indication. Investment Banks/Advisors: Bank of America Merrill Lynch; Credit Suisse Group (Abide Therapeutics Inc.)

MERCK & CO. INC. PELTON THERAPEUTICS INC.

Merck & Co. Inc. will pay \$1.05bn in cash up front to acquire privately held cancer drug developer **Peloton Therapeutics Inc.** The deal also includes up to \$1.15bn in earn-outs based on regulatory and sales achievements. (May)

Through the acquisition, Merck gains Peloton's small-molecule candidates targeting hypoxia-inducible factor-2a (HIF-2a) including lead project PT2977, which is in Phase II for von Hippel-Lindau (VHL) disease-associated renal cell carcinoma, Phase II in combination with cabozantinib for metastatic RCC, and Phase I/II dose escalation/expansion studies for mRCC and glioblastoma multiforme. (The company

is also working on non-cancer indications with the compound. It is in preclinical studies for pulmonary arterial hypertension.) PT2977 is currently the only HIF-2a inhibitor in clinical trials. Merck boosts its cancer (and kidney cancer in particular) offerings through the acquisition. The Big Pharma's PD-1 checkpoint inhibitor *Keytruda* (pembrolizumab) is a sales leader in the immuno-oncology space, garnering over \$7bn in 2018. The drug is marketed for advanced RCC and a variety of other solid tumors, and is also in combination trials for the disease. Peloton was formed in 2011 and brought in over \$300m through venture rounds. The company had just filed for an IPO in April, in which it hoped to raise up to \$159m. Its investor syndicate (including Foresite, Reditex, The Column Group, Tichenor Ventures, Topspin Fund, and Nextech Invest) will now see a much more impressive exit via the Merck acquisition. Investment Banks/Advisors: Credit Suisse Group (Merck & Co. Inc.); Centerview Partners LLC (Peloton Therapeutics Inc.)

PFIZER INC. THERACHON AG

Pfizer Inc. is acquiring closely held rare disease-focused **Therachon AG** for \$340m up front, plus up to \$470m in earn-out payments tied to the development and commercialization of TA46 for achondroplasia. (May) TA46 is a fibroblast growth factor receptor 3 antagonist being developed as a weekly subcutaneous injection for children and adolescents living with achondroplasia, a form of short-limbed dwarfism for which there are no approved therapies. Therachon completed Phase I trials and the candidate has orphan drug designation from both the FDA and EMA. Therachon's pipeline includes one other compound, apraglutide (FE203799). However, Pfizer won't own the drug because prior to the acquisition closing, the company will spin-off apraglutide into a separate and independent entity. Pfizer Ventures will hold a minority stake in the yet-to-be-named firm. Apraglutide is a once-weekly glucagon-like peptide 2 receptor agonist currently in Phase II trials for short bowel syndrome. Therachon gained apraglutide through its October 2018 acquisition of **GlyPharma Therapeutics**. (The drug originated at **Ferring** and was exclusively licensed to GlyPharma in 2012.) Investment Banks/Advisors: Goldman Sachs & Co. (Therachon AG)

ALLIANCES

ADAPTIMMUNE THERAPEUTICS PLC ALPINE IMMUNE SCIENCES INC.

Adaptimmune Therapeutics PLC and **Alpine Immune Sciences Inc.** will work together to discover and develop next-generation T-cell therapies for cancer based on Adaptimmune's secreted and transmembrane immunomodulatory

protein (*SIP* and *TIP*) technologies. (May) Adaptimmune pays \$2m up front, in addition to research funding and up to \$288m in development and commercialization milestones, plus low-single digit royalties (*Strategic Transactions* estimates 1-3%). *SIP* and *TIP* help modulate the immune synapse and enhance persistence and efficacy of engineered T-cell therapies. The partners will work together to discover and develop *SIP* and *TIP* candidates that could potentially enhance the anti-tumor response of Adaptimmune's SPEAR (Specific Peptide Enhanced Affinity Receptor) T cells, which are engineered to target and destroy solid tumors. Adaptimmune gets an option to license exclusive global rights to develop and sell SPEAR T-cell projects that incorporate a *TIP* or *SIP* candidate.

ASTRAZENECA PLC

Acerta Pharma BV

FORTY SEVEN INC.

Acerta Pharma BV (Astrazeneca PLC's blood cancer R&D center of excellence) and Forty Seven Inc. penned a trial collaboration to investigate the combination of Forty Seven's CD47 antibody Hu5F9-G4 (5F9) in combination with rituximab together with Acerta's *Calquence* (acalabrutinib) for diffuse large B-cell lymphoma (May)

Forty Seven already has 5F9 in Phase II trials as a combo therapy with rituximab, a CD20 antagonist. Those studies are returning positive results, and now the partners will add in acalabrutinib, Acerta's BTK inhibitor on the market for mantle cell lymphoma. (It is also in studies for leukemia, non-Hodgkin's lymphoma, and solid tumors.) The triplet combination approach could provide a treatment that takes advantage of the effectiveness of a BTK inhibitor for B-cell lymphoma while also activating the innate immune system.

ASTRAZENECA PLC INSTITUT MERIEUX

Transgene SA

Transgene SA and AstraZeneca PLC partnered to discover and develop five oncolytic Vaccinia virus candidates based on Transgene's *Invir.IO* next-gen viral platform. (May)

Invir.IO is based on Transgene's engineered Vaccinia virus strain (TK-, RR-) and allows the company to design multifunctional oncolytic viruses. Under terms of the deal, Transgene is responsible for in vitro preclinical studies, after which point AZ will select transgenes to be encoded within the virus and carry out in vivo preclinical work. The Big Pharma can exercise options to exclusively develop and commercialize up to five of the armed oncolytic candidates. Transgene gets \$10m up front and up to \$3m in payments for preclinical achievements, in addition to option exer-

cise payments, development and sales milestones, and royalties.

BOEHRINGER INGELHEIM GMBH GUBRA APS

As a follow-on to their September 2017 deal, **Boehringer Ingelheim GmbH and Gubra ApS** are again partnering in obesity. (May)

Through the current tie-up, BI could provide up to €240m (\$268m) in up-front payments and development and commercialization milestones, plus up to double-digit royalties on worldwide net sales. The aim of this new joint collaboration is to develop poly-agonist peptides for obesity through the combination of each company's complementary strengths. Gubra's expertise in the design, synthesis, characterization, and testing of therapeutic peptides (focused in the metabolic space) is based on an approach that incorporates in vivo pharmacology, peptide chemistry, molecular pharmacology, histology, 3D imaging, stereology, next-generation sequencing, bioinformatics, and ex vivo assays. Through its extensive pipeline and marketed drugs in the cardiometabolic disease area, BI has established R&D proficiency. The Big Pharma's SGLT2 inhibitor *Jardiance* (empagliflozin) is the best-selling drug in the diabetes class, with worldwide revenues of \$1.6bn for 2018. The ongoing 2017 partnership, which BI claims has already achieved important milestones, seeks to identify peptides capable of regulating food intake. Under that deal, Gubra stands to get up to €250m in up-front and success-based development and sales milestones from BI, in exchange for the licensing of any resulting candidates from the joint R&D program.

CENTREXION THERAPEUTICS CORP. ELI LILLY & CO.

Eli Lilly & Co. licensed exclusive global rights to develop and sell the non-opioid pain candidate CNTX0290 from **Centrexion Therapeutics Corp.** (May)

CNTX0290 is a somatostatin receptor type 4 (SSTR4) agonist in Phase I studies for chronic pain associated with inflammatory, neuropathic, and mixed pain conditions. Centrexion licensed the candidate from **Boehringer Ingelheim** in 2016 (along with two other analgesics) and will now entrust Lilly and its experience with pain management therapies to continue developing and eventually commercialize the project. Lilly pays \$47.5m up front, up to \$575m in development and regulatory milestones, \$375m in sales milestones, and tiered high-single to low-double digit royalties. The partners could amend the deal at a later time to include co-promotion rights for Lilly in the US. Lilly adds CNTX0290 to a pain pipeline that includes an antibody in Phase I, tanezumab in Phase III for chronic lower back pain, can-

cer pain, and osteoarthritic pain, and two candidates awaiting regulatory approval—galcanezumab for cluster headache pain and lasmitidan for migraine.

CINCOR PHARMA INC. ROCHE

Roche licensed **CinCor Pharma Inc.** exclusive worldwide rights to the Phase I highly selective aldosterone synthase inhibitor CIN107. (May)

CinCor takes over development, manufacturing, and commercialization of CIN107 for treatment-resistant hypertension and primary aldosteronism, a disorder in which the adrenal glands overproduce the hormone aldosterone, leading to hypertension. There is also evidence that build up of aldosterone causes end-organ damage, such as cardiovascular remodeling and renal injury. Concurrent with the license agreement, CinCor closed a \$50m Series A round from Sofinnova Investments, Sofinnova Partners, and 5AM Ventures. The money will support CIN107 as it moves into a Phase I multiple-ascending dose trial (a single ascending-dose study was previously done) toward Phase II proof-of-concept trials. Roche had three aldosterone synthase inhibitors in its pipeline: RG7641, RO6836191, and an unnamed candidate. In aggregate, they were in development for several conditions including renal failure, heart failure, and primary hyperaldosteronism, but the Big Pharma discontinued work. It's unclear which one is now CIN107.

CSTONE PHARMACEUTICALS CO. LTD. NUMAB THERAPEUTICS AG

Numab Therapeutics AG granted **CStone Pharmaceuticals Co. Ltd.** exclusive rights to develop and sell its immunotherapy candidate NDo21 in China, Hong Kong, Macau, Taiwan, South Korea, and Singapore. (May)

NDo21 is a tri-specific antibody (targets PD-L1, 4-1BB, and HSA) in preclinical cancer studies. The candidate is designed to prevent liver toxicities commonly seen in patients treated with traditional 4-1BB-agnostic antibodies by binding to 4-1BB and activating T-cells only when it engages with PD-L1 on tumor cell surfaces. CStone agreed to fund development through an initial Phase Ib trial, with no further financial obligations, and will market the candidate in the licensed territories. The company's immuno-oncology pipeline has candidates in various stages for both solid and blood cancers. CStone also has partnerships underway with **Agios** (rights in Greater China to *Tibsovo* (ivosidenib), approved by the FDA last year for relapsed/refractory AML with an IDH1 or IDH2 mutation) and **Blueprint** (Greater China rights to multiple combination therapies).

CUMULUS ONCOLOGY LIGAND PHARMACEUTICALS INC.

Ligand Pharmaceuticals Inc. granted Cumulus Oncology exclusive global rights to develop and sell the preclinical cancer candidate VER250840. (May)

Cumulus pays money up front, up to \$76m in total milestones, and royalties ranging from the mid-to-high single digits. (*Strategic Transactions* estimates 4-9%.) If Cumulus completes specific financing-related events, Ligand could also receive an additional fee payable in cash or equity in Cumulus. VER250840 is a checkpoint kinase 1 (Chk1) inhibitor that has potential in multiple tumor types as both a monotherapy and in combination with cytotoxic drugs. Cumulus plans to work with **LXRepair** (develops functional biomarker-based oncology diagnostics for drug discovery) and **Intelligent Omics** (AI company focusing on biomarker identification) in the design of further trials for the candidate.

CURADEV PHARMA PVT. LTD. TAKEDA PHARMACEUTICAL CO. LTD.

Curadev Pharma Pvt. Ltd. granted Takeda Pharmaceutical Co. Ltd. rights to develop and sell its STING (Stimulator of Interferon Genes) agonist molecule CDR5500 for solid tumors. (May)

Curadev's STING agonist program aims to stimulate an innate immune response in tumors lacking a T-cell infiltrate. CRD5500, Curadev's lead STING agonist, efficiently activates the immune system and has potential to combine with anti-PD-L1/anti-CTLA4/IDO-TDO antibodies to form antibody-drug conjugates for even greater effectiveness. (It has been successfully conjugated with Genentech's *Herceptin* (trastuzumab).)

EXELIXIS INC. ICONIC THERAPEUTICS INC.

Exelixis Inc. entered an exclusive option to agreement for rights to **Iconic Therapeutics Inc.**'s second-generation antibody-drug conjugate ICON2 for solid tumors. (May)

ICON2 targets Tissue Factor, which is highly expressed on tumor cells and in the tumor microenvironment. Iconic has designed the candidate in such a way that it does not interfere with blood coagulation in the way that an active competing candidate does. The company plans to bring the project into IND-enabling studies later this year. Exelixis pays \$7m up front and also committed to cover preclinical development funding. At the time of IND application, the company can exercise its option to take over all development and commercialization activities. It would pay an option exercise fee and be on the line for development, regulatory, and sales milestones, as well as royalties. The deal is the second in a week for Iconic (following a collaboration under which it gained

non-exclusive rights to use **Zymeworks**'s *ZymeLink* ADC program in its continued work with ICON2), and is the company's first strategic deal in the cancer space. It is also working on a program targeting Tissue Factor in macular degeneration.

GILEAD SCIENCES INC. GOLDFINCH BIO INC.

Goldfinch Bio Inc. and Gilead Sciences Inc. penned a collaboration surrounding the development of new treatments for diabetic kidney disease (DKD) and certain orphan kidney diseases. (May)

Under terms of the deal, Goldfinch will use its *Kidney Genome Atlas (KGA)* kidney disease registry to identify and validate targets, and will also apply its platform of human induced pluripotent stem cell-derived kidney cell and kidney organoids for target validation. *KGA* combines genomic, transcriptomic, and proteomic data with thousands of profiles of patients with kidney disease in an effort to discover targets, predict patient therapeutic response, and identify subgroups of patients with kidney disease for therapeutic intervention. Goldfinch will expand the scope of *KGA* to include DKD and orphan diseases. It will lead discovery and development activities until Gilead exercises its option for exclusive global rights to resulting candidates. Goldfinch retains an option to lead development and co-promote projects aimed at specific undisclosed kidney disease targets, and to equally share in US profits for certain products. Gilead pays \$55m up front (including a \$5m equity investment), \$54m in R&D support for development of the *KGA* platform for DKD, and up to \$1.95bn in total milestones for the first five compounds to come out of the deal, plus tiered royalties. The companies will share development costs.

GLENMARK PHARMACEUTICALS LTD. Glenmark Therapeutics Inc. OTONOMY INC.

Under a multi-year deal, **Otonomy Inc.** licensed **Glenmark Therapeutics Inc.** exclusive rights to co-promote in the US its *Otiprio* (ciprofloxacin) otic suspension for treating acute otitis externa (AOE). Otonomy retains commercial rights in all other indications. (May)

Glenmark Therapeutics will pay Otonomy an annual co-promotion fee and reimburse a proportion of product support expenses. Otonomy will retain a share of the adjusted gross profits from *Otiprio* sales. The drug is indicated for AOE patients ages six months and older due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Glenmark will promote the product to ENT specialists in the US and its territories. *Otiprio* will fit nicely into the company's respiratory portfolio led by *Ryaltis* (olopatadine hydrochloride/mometasone furoate) nasal spray, which is currently under review with the

FDA for treating seasonal allergic rhinitis in patients ages 12 and older.

HANX BIOPHARMACEUTICALS INC. ONCONOVA THERAPEUTICS INC.

Onconova Therapeutics Inc. granted HanX Biopharmaceuticals Inc. exclusive rights to develop and sell rigosertib in Greater China. HanX also gets nonexclusive manufacturing rights. (May)

Onconova gets \$6m up front (\$4m cash (\$2m immediately and \$2m in escrow) plus a \$2m equity investment) and could also receive up to \$45.5m in development, regulatory, and sales milestones, as well as royalties up to double digits. Rigosertib is in Phase III trials for higher-risk myelodysplastic syndrome (HR-MDS) and in additional studies for leukemia and lung cancer. HanX notes that the candidate is complementary to its own PD-1 antibody HX008; the company plans to conduct combination trials for non-small cell lung cancer with HX008 and rigosertib, and will also join Onconova's planned INSPIRE trial combining rigosertib with azacitidine for patients in China with HR-MDS. This is the second tie-up for Onconova and HanX. The two came together in late 2017 in a deal that granted HanX Chinese rights to Onconova's preclinical CDK4/6 and ARK5 inhibitor ON123300.

ICONIC THERAPEUTICS INC. ZYMEWORKS INC.

Zymeworks Inc. granted **Iconic Therapeutics Inc.** non-exclusive rights to use its *ZymeLink* antibody-drug conjugate platform to develop its ICON2 Tissue Factor ADC for cancer. (May)

ZymeLink is a suite of protein site-specific conjugation technologies and customizable cleavable and non-cleavable linkers. The platform allows for the production of homogeneous drug products, maintains stability, and provides for the efficient release of toxic payloads to target cells following internalization. Iconic is developing therapies that target diseases where Tissue Factor is overexpressed. It plans to enter IND-enabling studies with its ICON2 during 2019, noting that its project is not dose limiting like one of its competitors, since Iconic's monoclonal antibody doesn't interfere with blood clotting. Under terms of the deal, the company will pay development and sales milestones, as well as tiered sales royalties. Zymeworks has co-promotion rights in exchange for increased royalties, though if Iconic out-licenses its project, Zymework's co-promotion rights will be replaced with revenue sharing and royalties on any partners' sales.

IMMUNGENE INC. SPECTRUM PHARMACEUTICALS INC.

Spectrum Pharmaceuticals Inc. licensed exclusive global rights to **ImmunGene Inc.**'s *Focused Interferon Therapeutics*

(FIT) antibody-interferon fusion drug delivery platform and two related early-stage cancer candidates. (May)

Spectrum paid \$3m up front and will make up to \$156m in development, regulatory, and sales milestone payments, plus high-single digit royalties. (*Strategic Transactions* estimates 7-9%.) The FIT technology (originally developed at UCLA) fuses interferon with monoclonal antibodies targeting specific tumor antigens and is designed to produce compounds that retain the potency and efficacy of interferons while reducing interferon-associated toxicity. In addition to FIT, Spectrum also takes on rights to an antibody-interferon fusion candidate against CD20 in Phase I for relapsed/refractory non-Hodgkin lymphoma, and a fusion molecule directed against GRP49 for solid and blood cancers. There are currently no approved therapies targeting GRP94. Spectrum's rights for both candidates cover all cancer indications; the company's pipeline holds projects for solid tumors, but does not display any for blood cancers.

JIANGSU HANSOH PHARMACEUTICAL GROUP CO. LTD.

VIELA BIO INC.

Viela Bio Inc. granted **Jiangsu Hansoh Pharmaceutical Group Co. Ltd.** (Hansoh Pharma) rights to develop and sell the monoclonal antibody inebilizumab in China. (May)

Viela gets money up front, up to \$220m in development, regulatory, and commercialization milestones, plus tiered royalties. Inebilizumab targets CD19 and is in Phase III studies for the autoimmune disease neuromyelitis optica spectrum disorder (NMOSD); it could also have potential in other autoimmune, inflammatory, and blood cancer indications. The candidate was granted Breakthrough Therapy designation by the FDA in April, and Viela expects to file a BLA later this year. Viela was spun out of **AstraZeneca's MedImmune LLC** in 2018 and tasked with developing inebilizumab and five other autoimmune and inflammatory disease compounds. Hansoh will now work on inebilizumab in China, alongside its other projects in therapy areas including CNS, oncology, infectious disease, diabetes, cardiovascular conditions, and GI diseases.

KYMERA THERAPEUTICS INC. VERTEX PHARMACEUTICALS INC.

In a four-year agreement, **Vertex Pharmaceuticals Inc.** and **Kymera Therapeutics Inc.** are teaming up to develop small-molecule protein degraders against multiple targets aimed at serious specialty diseases. (May)

Kymera will perform research activities in multiple targets and once a candidate is selected for clinical development, Vertex has the option to exclusively license

molecules against the designated target. Vertex will pay Kymera \$70m up front, which includes an equity investment, and could shell out over \$1bn in development, regulatory, and commercial milestones for up to six programs. Kymera is also eligible for tiered sales royalties. Kymera will use its *Pegasus* drug discovery platform consisting of informatics-driven target identification, E3 ligases and ligands, ternary complex predictive modeling and degradation tools, and whole-cell proteomics capabilities. Targeted protein degradation causes the body's ubiquitin proteasome system to degrade disease-causing proteins not addressed elsewhere. The deal allows Vertex entry into the competitive protein degradation field. **C4 Therapeutics** and **Arvinas** are two of several biotechs focused in the space.

NOVARTIS AG TAKEDA PHARMACEUTICAL CO. LTD.

Further boosting its ophthalmic pharmaceuticals portfolio, **Novartis AG** agreed to acquire **Takeda Pharmaceutical Co. Ltd.**'s dry eye drug *Xiidra* (lifitegrast) 5% topical solution and all assets associated with it. (May)

Novartis will provide an up-front payment of \$3.4bn as well as potential milestones of up to \$1.9bn. *Xiidra* (SAR1118) was approved in the US in 2016 and in Canada last year, and awaits European clearance (an MAA was submitted in December 2018, with a decision anticipated during the first half of this year). The drug originated with **Sunesis**, which discontinued its development and then granted worldwide rights to SARcode Bioscience under a 2007 deal. SARcode was acquired by **Shire PLC** for \$160m in 2013 and Takeda since bought Shire in a \$79bn transaction last year. As part of the current deal, Novartis is also taking on 400 former Shire employees associated with the product, which competes with already-approved prescription dry-eye drops *Restasis* (cyclosporine) (sold by **Allergan**). However, *Xiidra* is indicated to treat both the signs and symptoms of dry eye, inhibiting inflammation by blocking the binding of two key cellular surface proteins--lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1). The addition will complement Novartis' existing dry eye portfolio, which already includes the *Tears*, *Systane*, and *Tear-Gel* brands. Novartis also has a pipeline of numerous ophthalmology compounds, including dry eye candidates lubricin (ECF843; Phase III), in-licensed from US biotech **Lubris BioPharma** in 2017, and preclinical BL1230 (a selective cannabinoid receptor type 2) under development with **BioLineRx** (under a 2014 collaboration). Takeda is divesting the drug to focus on its core business areas (gastroenterology, rare diseases, plasma-derived therapies, oncology, and neuroscience) following its buy of

Shire. In a concurrent transaction, Takeda is also selling its *TachoSil* fibrin sealant patch to **Ethicon** for \$400m. Investment Banks/Advisors: Evercore Partners (Takeda Pharmaceutical Co. Ltd.)

PHATHOM PHARMACEUTICALS TAKEDA PHARMACEUTICAL CO. LTD.

Takeda Pharmaceutical Co. Ltd. and Frazier Healthcare Partners launched a new company, **Phathom Pharmaceuticals**, which has been granted an exclusive license to develop and sell Takeda's GI drug vonoprazan in the US, Canada, and Europe. (May) Terms of the deal include an up-front cash payment and equity investment, in addition to milestones and royalties. Vonoprazan (marketed as *Takecab*) is an oral active potassium competitive acid blocker indicated for conditions of excessive stomach acid. Phathom will conduct Phase III US trials with the candidate for gastroesophageal reflux disease (GERD) and in combination with antibiotics for eradication of *H. pylori*. Takeda keeps rights in certain Asian markets, and will also continue marketing it in Japan with promotion partner **Otsuka**. Concurrent with the licensing, Phathom completed a crossover financing round of \$90m led by Frazier, and also entered into a \$50m debt facility with SVB.

ROCHE

Genentech Inc.

PARVUS THERAPEUTICS INC.

For the second time, **Parvus Therapeutics Inc.** teamed up with a Big Pharma partner, this time with **Roche's Genentech Inc.** to develop, manufacture, and sell treatments worldwide for inflammatory bowel disease (IBD), autoimmune liver diseases, and celiac disease. The partners will create drug candidates using Parvus' *Navacim* platform. (May) Parvus will conduct preclinical through Phase I studies, and Genentech will take over the remaining clinical trials, global regulatory filings, and worldwide commercialization. Genentech is responsible for an up-front fee and research, development, and commercialization milestones per disease, all of which could exceed \$800m, plus sales royalties. *Navacims*--nanoparticles coated with peptide-major histocompatibility complexes--instruct disease-causing effector T-cells to convert into and expand the population of regulatory T-cells (Tregs), which can induce immune tolerance. The technology is based on the work done by Parvus' CSO Pere Santamaria, MD, PhD, and Julia McFarlane at the **University of Calgary**. In 2017, **Novartis** signed an agreement to use the *Navacim* platform in Type I diabetes. Immune disease has been one of Roche's main focus areas, especially as biosimilars to its rheumatoid arthritis product *Rituxan* have been approved (*Rituxan* is also sold for oncology indications). The company's next immunology filing could be in 2021 with etrolizumab, an antibody targeting the

beta 7 integrin subunit for ulcerative colitis. Within the last two years, Roche/Genentech have also done alliances around IBD with **Microbiotica** and **Boehringer Ingelheim**.

SKYHAWK THERAPEUTICS INC. TAKEDA PHARMACEUTICAL CO. LTD.

Skyhawk Therapeutics Inc. will use its *SkySTAR* RNA expression correction platform to discover new neurodegenerative disease candidates for **Takeda Pharmaceutical Co. Ltd.** (May)

Takeda pays money up front, milestones, and royalties, and gets exclusive global rights to develop and commercialize resulting candidates directed at multiple targets. The *SkySTAR* (*Skyhawk Small molecule Therapeutics for Alternative splicing in RNA*) technology utilizes information from computational, kinetic, and structural models of RNA to develop drug candidates that can correct an RNA splicing defect called exon skipping, which results in RNA mutations that cause diseases including cancer and neurological conditions. Takeda is Skyhawk's second new partner this year; in January, a similar deal was penned with **Biogen**, which paid \$74m up front for options to license *SkySTAR* candidates for neurological diseases including multiple sclerosis and spinal muscular atrophy. **Celgene** also hopes to land some *SkySTAR* projects through its June 2018 deal. It paid \$60m up front for options to potential therapies for conditions including ALS, Huntington's disease, and others.

FINANCINGS

ADMA BIOLOGICS INC.

ADMA Biologics Inc. (developing plasma-derived biologics for immune deficiencies and infectious diseases) netted \$48.6m through the follow-on sale of 12.9 million common shares (including full exercise of the overallotment) at \$4 each. The company will use the funds to launch its *Asceniv* for primary humoral immunodeficiency disease (PIDD) in H2 2019, to relaunch *Bivigam* for PIDD, to expand its manufacturing facility, to obtain raw materials needed for manufacturing *Asceniv* and *Bivigam*, and to expand its plasma collection facility network. (May)

Investment Banks/Advisors: Jefferies & Co. Inc.; Oppenheimer & Co. Inc.; Raymond James & Associates Inc.

AMICUS THERAPEUTICS INC.

Amicus Therapeutics Inc. (developing drugs for rare and orphan metabolic diseases) netted \$164.5m through a public offering of 16.3 million common shares at \$10.75. Some of the proceeds will support development activities for the company's gene therapy pipeline as well as manufacturing for gene therapy candidates and the Pompe disease bio-

logic AT-GAA. (May)

Investment Banks/Advisors: Goldman Sachs & Co.; JP Morgan Chase & Co.; SVB Leerink

APTOSE BIOSCIENCES INC.

Aptose Biosciences Inc. (cancer drug development) netted \$17.2m through a public offering of 10 million common shares at \$1.85. Some of the proceeds will support preclinical candidate CG806 for acute myeloid leukemia and APT0253, in Phase I for AML and myelodysplastic syndrome. (May)

Investment Banks/Advisors: Canaccord Genuity Inc.; HC Wainwright & Co.; RBC Capital Markets

ARMATA PHARMACEUTICALS INC.

The reverse merger between AmpliPhi and C3J has been completed to create **Armata Pharmaceuticals Inc.**, which concurrently raised \$10m in a financing to C3J shareholders. The merged entity will develop phage-based therapies aimed at antibiotic-resistant infections. The new money combined with Armata's \$6m in cash will help support its preclinical and clinical development pipeline. Its lead program is Phase Ib/II-ready APSA01 for *Staphylococcus aureus*; an IND filing is expected this year. (May)

ATHENEX INC.

Athenex Inc. grossed \$100m in a private placement of 10 million shares at \$10 apiece (a 4% discount) to Perceptive Advisors, Avoro Capital Advisors (formerly known as venBio Select Advisor), and OrbiMed. The company will use the proceeds to support clinical development, regulatory, and commercialization activities of Phase I/II *Oraxol* (paclitaxel/HM30181A, a gastrointestinal tract-specific P-glycoprotein pump inhibitor) for solid tumors, and regulatory activities surrounding KX2391 topical ointment (Phase III for actinic keratosis (with a 70% likelihood of approval in this indication, 8% above average) and also under development for oncology uses). Athenex will also put some funds toward manufacturing infrastructure. (May)

AXCELLA HEALTH INC.

Axcella Health Inc. (therapies addressing dysregulated metabolism) netted \$66.4m in its initial public offering of 3.57 million common shares at \$20 each, the low end of its anticipated range. (May)

Investment Banks/Advisors: Goldman Sachs & Co.; JP Morgan & Co.; SVB Leerink

BICYCLE THERAPEUTICS LTD.

Peptide therapeutics developer **Bicycle Therapeutics Ltd.** competed its IPO on the Nasdaq, netting \$56.9m through the sale of 4.33 million American Depository

Shares (representing 4.33 million ordinary) at \$14 apiece, the low end of the company's intended \$14-16 range. (May)

Investment Banks/Advisors: Canaccord Genuity Inc.; Goldman Sachs & Co.; Jefferies & Co. Inc.; Piper Jaffray & Co.

BRIDGEBIO PHARMA INC.

BridgeBio Pharma Inc. filed for its initial public offering on the Nasdaq. (May)

Investment Banks/Advisors: BMO Financial Group; Goldman Sachs & Co.; JP Morgan & Co.; Jefferies & Co. Inc.; KKR; Mizuho Bank Ltd.; Piper Jaffray & Co.; Raymond James & Associates Inc.; SVB Leerink

CAN-FITE BIOPHARMA LTD.

Can-Fite BioPharma Ltd. (developing A3 adenosine receptor-targeting therapies for autoimmune and inflammatory diseases and cancer) netted \$5.64m a registered direct offering of 1.5 million American Depositary Shares (representing 45 million ordinary shares) at \$4 per ADS. Investors also received five-and-one-half year warrants to buy 1.5 million ADSs at \$4. HC Wainwright was the placement agent. (May)

Investment Banks/Advisors: HC Wainwright & Co.

CLOVIS ONCOLOGY INC.

Clovis Oncology Inc. entered into a non-dilutive financing agreement with TPG Sixth Street Partners, the proceeds of which will reimburse the company for a clinical trial evaluating its ovarian cancer drug *Rubraca* (rucaparib) with *Opdivo* (nivolumab). (Clovis and **BMS** entered into a trial collaboration for the combo therapy in 2017.) (May)

CORTEXYME INC.

Cortexyme Inc. (diagnosis and treatment of neurodegenerative diseases) netted \$80.2m in its initial public offering of 5 million shares (including the overallotment) at \$17.00, the mid-point of its anticipated range. (May)

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

FORTRESS BIOTECH INC.

Mustang Bio Inc.

Mustang Bio Inc. netted \$29.7m through a public offering of 7.9m common shares (including the overallotment) at \$4. The gene/cell therapy firm also recently received \$15m in a venture debt financing signed last month with Horizon Technology; the agreement totals \$20m, and Mustang can draw down the remaining \$5m pending achievement of certain milestones. (May)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; HC Wainwright & Co.; Oppenheimer & Co. Inc.; Roth Capital Partners (Mustang Bio Inc.)

GALECTIN THERAPEUTICS INC.

Galectin Therapeutics Inc. (chronic liver and skin diseases and cancer) raised \$44.5m through a rights offering which resulted in the issuance of 10.4 million common shares at \$4.28 per share. Investors also received seven-year warrants to purchase 2.6 million shares at \$7. A portion of the proceeds will support a Phase III trial with GRMDo2 in nonalcoholic steatohepatitis patients without esophageal varices. (May)

GOSSAMER BIO INC.

Gossamer Bio Inc. (immunology, inflammation, and oncology therapeutics) entered into a \$150m debt facility with MidCap Financial, through which the company received \$30m at closing and can draw down on the remaining \$120m in three tranches (\$40m, \$30m, and \$50m, respectively) by July 31, 2021. Each loan bears interest at an annual rate equal to the sum of one-month LIBOR plus 6.15%, subject to a 2% LIBOR floor. Gossamer will use the proceeds to support continued R&D and general corporate needs. (May)

IDEAYA BIOSCIENCES INC.

Ideaya Biosciences Inc. (cancer drug development using molecular diagnostics) netted \$46.5m through its initial public offering of 5 million common shares at \$10, well below the company's intended range of \$13-15. (May)

Investment Banks/Advisors: Citigroup Inc.; JP Morgan Chase & Co.; Jefferies & Co. Inc.

INSMED INC.

Respiratory-focused **Insmed Inc.** netted \$236.3m through the sale of 9.6 million common shares at \$26 each. The company will use the funds to commercialize its *Arikayce* (amikacin liposome inhalation suspension) for patients with nontuberculous mycobacteria lung disease caused by *Mycobacterium avium* complex (MAC); for ongoing clinical trials of *Arikayce* for MAC lung disease; for continued clinical development of INS1007 for non-CF bronchiectasis and granulomatosis with polyangiitis, and INS1009 for pulmonary arterial hypertension; to invest in increased third-party manufacturing capacity for *Arikayce*; and for business expansion activities in Europe and Japan. (May)

Investment Banks/Advisors: Credit Suisse Group; Goldman Sachs & Co.; HC Wainwright & Co.; Morgan Stanley & Co.; SVB Leerink; Stifel Nicolaus & Co. Inc.

INTERCEPT PHARMACEUTICALS INC.

Intercept Pharmaceuticals Inc. (developing treatments for primary biliary cholangitis, NASH, and primary sclerosing cholangitis) netted \$383.4m through concurrent public offerings of common shares and convertible debt. (May)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Credit Suisse Group; Goldman Sachs & Co.; JMP Securities LLC; Jefferies & Co. Inc.; Needham & Co. Inc.; Oppenheimer & Co. Inc.; RBC Capital Markets; Robert W. Baird & Co. Inc.; Roth Capital Partners; UBS Investment Bank

INTERCEPT PHARMACEUTICALS INC.

Liver disease therapeutics company **Intercept Pharmaceuticals Inc.** grossed \$10m through the private placement of 119,760 common shares at \$83.50 (a 5% discount) to existing shareholder Samsara BioCapital. The PIPE was concurrent with public offerings of common shares and convertible notes that netted \$383.4m for the company. (May)

MAGENTA THERAPEUTICS INC.

Magenta Therapeutics Inc. (targeted treatments to improve bone marrow transplantation) netted \$60.9m through the public offering of 4.9 million common shares (including the over-allotment) at \$13.25. Funds will support pipeline advancement, including MGTA145, a first-line mobilization treatment, into Phase II; work to bring stem cell therapy program MGTA456 into Phase III; and additional development projects. (May)

Investment Banks/Advisors: Cowen & Co. LLC; Goldman Sachs & Co.; JP Morgan Chase & Co.; Wedbush PacGrow Life Sciences

MERSANA THERAPEUTICS INC.

Mersana Therapeutics Inc. (antibody-drug conjugates for cancer) entered a \$20m non-dilutive term loan agreement with Silicon Valley Bank (SVB), which funded \$5m immediately. The remaining \$15m can be drawn down through August 31, 2020, with payments due by February 1, 2023 (interest only through August 31, 2020 and the remainder in equal installments of principal and interest). (May)

MILESTONE PHARMACEUTICALS INC.

Cardiovascular disease-focused **Milestone Pharmaceuticals Inc.** netted \$76.7m in its upsized initial public offering of 5.5 million common shares priced at \$15, the mid-point of its intended range. (May)

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

NEXTCURE INC.

Immunotherapy firm **NextCure Inc.** netted \$80.2m through its initial public offering of 5.75 million common shares (including the over-allotment) at \$15, the midpoint of the company's intended \$14-16 range. (May)

Investment Banks/Advisors: Bank of America Merrill Lynch; Morgan Stanley & Co.; Piper Jaffray & Co.

NOVAN INC.

Novan Inc. received \$12m in funding from **Ligand Pharmaceuticals Inc.** in exchange for tiered royalties of 7-10% and regulatory and commercial milestones of up to \$20m based on future North American sales of Novan's SB206, a nitric-oxide-based topical gel in Phase II molluscum contagiosum, a skin disease caused by the molluscipoxvirus, and any other Novan products used to treat molluscum. (May)

ONCOSEC MEDICAL INC.

OncoSec Medical Inc. netted \$10.3m through a public offering of common shares and warrants at a combined price of \$3.15. Investors bought 3.5 million common shares and also received five-year warrants to purchase 2.6 million common at \$3.45. The company is working on cytokine-based intratumoral immunotherapies and will use the proceeds for continued development, regulatory, and potential commercialization activities. (May)

Investment Banks/Advisors: Alliance Global Partners; Maxim Group LLC

REGULUS THERAPEUTICS INC.

Regulus Therapeutics Inc. (drugs targeting microRNAs) closed the first tranche of a private placement through which it grossed \$16.2m. The company sold 9.7 million common shares at \$1.205 (an 8% premium) together with five-year warrants to purchase 9.3 million shares at \$1.08, and also issued 415,898 non-voting Class A-1 convertible preferred shares (each convertible into 10 common) at \$10.80, along with five-year warrants for 4.16 million common at \$1.08. A second tranche of \$25.1m could be realized if the company announces plans by December 31, 2019 to recommence a Phase I multiple ascending dose trial of its RGLS4326 for autosomal dominant polycystic kidney disease (ADPKD). (May)

ROIVANT SCIENCES GMBH

Myovant Sciences Ltd.

Myovant Sciences Inc. (therapies for women's health and prostate cancer) netted \$117.5m through a public offering of 15.15 million common shares at \$8.25. Funds will support ongoing Phase III trials with lead candidate relugolix (the LIBERTY trial for uterine fibroids and heavy menstrual bleeding, and the HERO study for advanced prostate cancer), and will also be used to fund potential regulatory filings for the project. (May)

Investment Banks/Advisors: Cowen & Co. LLC; Evercore Partners; Goldman Sachs & Co.; JP Morgan Chase & Co. (Myovant Sciences Ltd.)

TRANSLATE BIO INC.

Translate Bio Inc. (messenger RNA therapeutics) grossed \$47.5m through

the private sale of 5.58 million common shares at \$8.50 each (a 14% discount) to several institutional accredited investors. According to the Form D, 22 investors participated. The company plans to use the funds for ongoing development of Phase I/II MRT5005 for cystic fibrosis and preclinical MRT5201 for ornithine transcarbamylase deficiency, and for additional R&D activities. Jefferies and SVB Leerink were the placement agents. (May)

Investment Banks/Advisors: Jefferies & Co. Inc.; SVB Leerink

TREVI THERAPEUTICS INC.

Trevi Therapeutics Inc. (developing nalbuphine ER for pruritic and neurologically mediated conditions) netted \$51.2m through its initial public offering of 5.5 million shares at \$10. The company had planned to sell 4.7 million shares at a \$14-16 range, when it announced the offering last month. Concurrent with the IPO, in a separate private placement from New Enterprise Associates, which bought 1.5 million shares at the IPO price, Trevi netted \$14m. (May)

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

TREVI THERAPEUTICS INC.

Concurrent with its \$51.2m IPO, **Trevi Therapeutics Inc.** netted \$14m in a separate private placement from New Enterprise Associates, which bought 1.5 million shares at the IPO price of \$10. The IPO underwriters--SVB Leerink, Stifel, BMO Capital, and Needham & Co.--were the placement agents. (May)

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

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

FINANCINGS

TWIST BIOSCIENCE CORP.

Synthetic DNA firm **Twist Bioscience Corp.** netted \$85.1m through a follow-on offering of 4.31 million common shares (including full exercise of the over allotment) at \$21 each. The company will use the proceeds for platform improvement and next-generation sequencing (NGS) activities; to expand commercial operations in the US, Europe, and Asia; for entry into the pharmaceutical biologics drug discovery and DNA data storage markets; and to establish NGS operations in China. This is Twist's first financing since going public in October 2018. (May)

Investment Banks/Advisors: Cowen & Co. LLC; Evercore Partners; JP Morgan & Co.; Robert W. Baird & Co. Inc.

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