

# In Vivo



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## PERSONALIZED MEDICINE

Treating The Individual Patient

illumina CSO Paints A Vision For  
The Future Of Precision Medicine

In Vivo's Quick Guide  
To Gene Therapy

Going Back To The Future  
To Treat Diabetes

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## Illumina CSO Bentley Paints A Vision For The Future Of Precision Medicine

ASHLEY YEO

Genomic medicine is coming of age. For Illumina chief scientific officer David Bentley, that not only means improved technology, accuracy and coverage of gene sequencing and a broadening into cancer, but also a better understanding among the wider population of disease and precisely the benefits that gene sequencing can bring to patients – actual and pre-symptomatic.

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## What Does It Take To Launch And Lead An Oncology Biotech Today?

LUCIE ELLIS

Oncolytic virus company Theolytics has emerged ready to raise a Series A round and get its preclinical assets into human trials by 2021. CEO Charlotte Casebourne talks to *In Vivo* about the challenge of standing out from the crowd in oncology, how viruses have evolved as a treatment approach in cancer, and how oncolytic viruses might be able to answer the cancer drug pricing conundrum.

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## Going Back To The Future To Treat Diabetes

WILLIAM LOONEY

Applied Therapeutics has a business model that defies the conventional wisdom about start-up success: reviving science abandoned by big pharma and financing from a narrow group of investors, dependent on the goodwill of a single academic institution; all in pursuit of a small molecule solution to one of the biggest, diversely complex and cost-defying challenges in chronic disease – the complications of diabetes.

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## Rgenix: A Cancer Start-Up's Resolve To Crack The Mystery Of Metastasis

WILLIAM LOONEY

Rgenix, a New York-based start-up co-founded by three prominent physician researchers, is taking aim at what it contends is the future of cancer treatment: finding drugs that shut off the biological chain reaction called tumor metastasis – the colonization of malignant cells throughout the body that ends up killing the majority of cancer patients.



MASOUD TAVAZOIE, RGENIX CEO

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## *In Vivo*'s Quick Guide To Gene Therapy

ALEX SHIMMINGS

Once the stuff of (largely implausible) science fiction, gene therapy is now a clinical reality and one that is taking an increasing share of the pharma R&D limelight. *In Vivo* takes a look at how these therapies work, how the field has emerged and where it is likely to go next.

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From The Editor



LUCIE ELLIS

*Personalised medicine is a move away from a “one size fits all” approach to the treatment and care of patients with a particular condition, to one which uses new approaches to better manage patients’ health and targets therapies to achieve the best outcomes in the management of a patient’s disease or predisposition to disease.*

This is how the UK’s National Health Service defines personalized medicine. In short, it is getting the right treatment to the right patient at the right time.

As a concept, personalized medicine is not new but the means to achieving it have evolved. Digital technologies and a better understanding of some diseases have advanced the way treatments can be targeted to patients. In this issue, *In Vivo* explores some key topics around the progress of personalized and precision medicine.

In 2018, 25 of the 59 new molecular entities approved by the FDA were classified as personalized therapies. This represents a significant rise over previous years, as shown in an infographic on page 8.

One of the greatest advancements for personalized medicine is genome sequencing. The cost of gene mapping has fallen exponentially, and it is now rarely necessary to map the whole genome. The first human genome to be mapped cost approximately \$3bn, by 2007 this had decreased to \$2m, and today it costs around \$1,000. In this issue, David Bentley, chief scientific officer of Illumina Inc., talks about how genomic medicine has come of age and its critical role within personalized medicine now and in the future. “Unlocking the power of the genome” is Illumina’s particular mission, he explains to Ashley Yeo (see page 10).

Opportunities lie ahead for an ever-better reading and understanding of the genome, and improving technology, accuracy and coverage. Rare disease was where genomic medicine started, but Illumina, as one example, is moving into cancer – a much bigger and more complicated field where genomics will gradually change the understanding of the disease. “Understanding the molecular mechanism of disease with the help of the genome part highlights what’s gone wrong, and thus the bit you want pharma to work on,” Bentley said.

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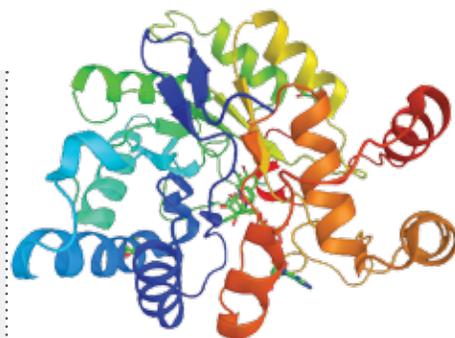
# Up-Front

## SNAPSHOTS FROM SEPTEMBER'S CONTENT

“Our ambition is to take a cancer and examine the whole genome, the complete panoply of mutations that has given rise to the cancer, read their profile with the signatures there in the DNA, and see how they have changed the DNA.”

– Illumina’s chief scientific officer David Bentley

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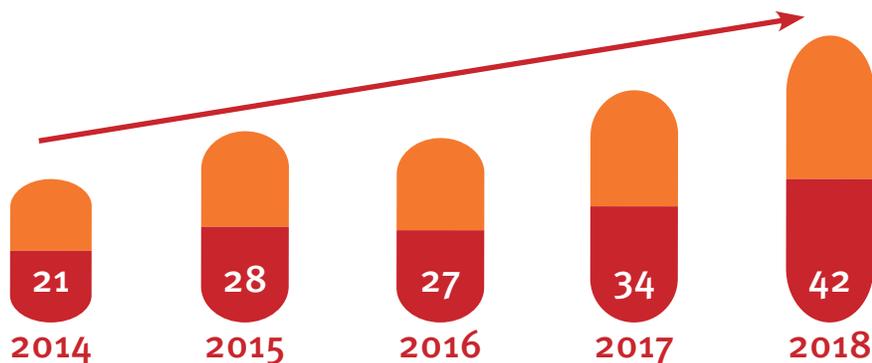


Finding treasure in discarded science is not without risks.

But interest in the strategy is growing now that big pharma has embraced external innovation and academic researchers to look for ways to progress beyond the lab work that often reflects years of commitment to a single pathogenic target. One start-up has even named itself after the concept: Applied Therapeutics Inc.

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The percentage of new drug approvals classed as “Personalized Medicines” is on the rise. PAGE 8



Despite development challenges, the therapeutic promise of gene therapy has proved a lure for many firms. There are currently around 425 unique companies – acting as originators or licensees – with development-stage candidates.

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“When price points rise to the level that they become a serious barrier to patient accessibility, this is a critically important challenge. Within the immunotherapy space we are seeing eye-watering prices, which is just one of the reasons viral therapies for cancer represent an attractive approach.”

– Charlotte Casebourne, CEO of Theolytics

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# ■ Around The Industry

## Made In China Gene Therapy: A Father's Quest To Save Son With UltraRare Condition



**Patient-driven drug development meets the old saying of "where there's a will, there's a way" in China, potentially the world's largest market for rare disease treatments.**

When Jian Shu's son Yue first started walking, he noticed that there was something not quite right, as the baby boy seemingly could not keep his body in balance.

Jian took Yue, whose name means happiness in Chinese, to see a doctor, who could not find what was wrong so ordered a gene sequencing test. The result showed that Yue had a type of progressive muscular dystrophy, a rare genetic condition that is usually inherited from a female carrier. But this was puzzling for Jian because when both he and his wife had gene testing they were found not to carry the gene that causes the condition. The reason why their son had dystrophy remained a mystery.

The most common form of muscular dystrophy, Duchenne muscular dystrophy (DMD), affects roughly one in 3,500 newborns, mostly boys. Symptoms start to show from age two and as the condition progresses, most boys have weaker muscular function compared to their peers and by 12 years old they usually lose the ability to walk. Most DMD sufferers die by the age of 20 to 30 due to respiratory function or heart failure.

There was no available treatment for DMD until 2016, when the US FDA approved Sarepta Therapeutics Inc.'s Exondys 51 (eteplirsen) for patients with the exon 51 skipping gene mutation. Later, another drug, Imflaza (deflazacort), developed by Marathon Pharmaceuticals LLC and later acquired by Sarepta Therapeutics Inc., gained approval.

There was still no cure for DMD, but hope started surfacing after several companies began testing experimental gene therapies in humans, notably Pfizer Inc. with PF-06939926, Sarepta with rAAVrh74.MHCK7.micro-dystrophin, jointly developed with the Nationwide Children's Hospital, and Solid Biosciences Inc.'s SGT-001.

This May, a breakthrough for gene therapy in general came when the US FDA gave the green light to Novartis AG's Zolgensma (onasemnogene abeparvovec) for another rare dystrophy, spinal muscular dystrophy. Developed by AveXis Inc., which was acquired by Novartis last year for \$8.7bn, it was the first such treatment approved for a muscular disorder. But it also came with a steep price tag, of \$2.1m

for the one-time treatment. (Also see "It's Official: Novartis SMA Gene Therapy Zolgensma Is World's Most Expensive Drug" - *Scrip*, 24 May, 2019.)

### GENE THERAPY GAINS PROMINENCE

Back in China, when Yue's condition progressed, Jian kept looking for answers and eventually learned about a company in Beijing developing vectors used in gene therapies for rare conditions. With a population of 1.3 billion and a large patient pool with rare genetic conditions, it is believed that China will need to develop its own gene therapies, given that such imported products will be simply too costly for what is a largely self-pay market.

This journey will not be easy. Firstly, there needs to be a clear and well-defined regulatory pathway, a necessity for any gene or cell therapy to get approved and launched in any given market. In China, there is currently a confusing "two-track mechanism" for such emerging technologies. This means that both qualified hospitals and biopharma firms can develop therapies, but under two separate regulatory oversight systems. For hospitals, the National Health Commission now oversees all matters governing how such products are developed. The National Medical Products Administration issues rules on how drug companies can develop cell and gene products.

The complicated system has industry regulatory professionals worried that it will lead to lower quality, redundant costs and wasted investment.

The Beijing vector company, FivePlus Molecular Research Institute, started out as a research service provider and in 2015 re-positioned itself to focus on the development of vectors, which carry and deliver re-engineered genes back into a patient's body. Not long after it started developing an adeno-associated virus

(AAV), FivePlus began collaborating with a physician in Wuhan-based Tongji Hospital, a top Class AAA facility in China's central metropolitan area. An eye doctor named Bin Li had specifically asked the company to develop a vector for an experimental study treating patients with Leber's hereditary optic neuropathy.

FivePlus was developing various vectors and AAV had shown superiority due to its safety profile. Physician Li came knocking on the door with the single aim of developing a gene therapy to treat the form of neuropathy, a genetic condition that leads to blindness. After initial trial and error, the study seemed to yield promising results. Between August 2011 and December 2015, a total of nine patients received the treatment at Tongji Hospital, following successful animal experiments. A three-year follow-up of the trial found no serious safety problems and "the results support the use of intravitreal rAAV2-ND4 as an aggressive maneuver in our clinical trial," noted a research paper summarizing the study published in *EBioMedicine* in August 2016. The encouraging results gave FivePlus's founder Xiaoyan Dong confidence to take on the case of Jian's son, who turned out to have a condition so rare that the diagnosis took a toll on the family and the father's quest to find a cure.

In 2016, gene therapy and its clinical use again entered Chinese researchers' consciousness when the Western China Hospital in Chengdu started the world's first CRISPR gene editing experiment in humans, treating lung cancer patients.

### ONE IN 10 MILLION

When Jian took Yue to visit FivePlus's office in Etown, a suburb of Beijing, his son was finally diagnosed with Emery-Dreifuss muscular dystrophy (EDMD), one of nine forms of muscular dystrophy. The diagnosis came after multiple trips to physicians and rounds of tests. Soon after taking on the case, FivePlus researchers started a primary document review on EDMD and related potential treatment options. In the meantime, the boy's whole gene sequencing results were sent out to other medical specialists in muscular dystrophies both inside and outside China.

After closer examination, Yue was eventually found specifically to have reducing body myopia (RBM) with FHL1 mutation. If

**RBM is so rare  
that there are  
few known cases  
around the world.  
In the US, the total  
known number of  
RBM cases is reported  
to be in the thirties,  
putting the occurrence  
rate at roughly  
one in 10 million.**

EDMD is a rare muscular dystrophy, RBM is so rare that there are few known cases around the world. After the diagnosis, Jian combed China to find other patients, and so far has found two other families with sufferers. In the US, the total known number of RBM cases is reported to be in the thirties, putting the occurrence rate at roughly one in 10 million.

### HELP FROM US FACILITIES

Due to its ultra-rare nature, RBM has attracted the attention of very few researchers around the world, posing an additional challenge to FivePlus researchers scouting for an animal model. Of two prospects they have found, only one has given them some hope. The Ju Chen Lab at the University of California San Diego (UCSD) was one of the places in the world conducting preclinical research on RBM with the FHL1 mutation. Professor Chen, upon being approached by the FivePlus Beijing team, agreed to provide mice from the lab for FivePlus to conduct the research.

After rounds of email communications and a payment to the school for the animals, a batch of FHL1 gene knockout mice generated in the US laboratory started their journey to China's capital.

Other than the UCSD team, the handful of physicians globally specialized in RBM included Carsten Bonnemann at

the Philadelphia Children's Hospital in Pennsylvania, who spends part of his time conducting research at the National Institutes of Health in Bethesda, MD. With slim hopes, Jian decided to seek out Bonnemann's help in diagnosing and treating his son, the determined father undaunted by the huge distance between Hangzhou and Philadelphia.

Working a job at a large national grocery chain in China, Jian had an insurance policy with China Pingan Insurance Co., which luckily covered his trip to seek medical help overseas. After days of back-and-forth arrangements, Jian embarked on the long-sought journey to take Yue to see Bonnemann.

Again, the diagnosis was confirmed. "The mutation that was found is very convincing for this diagnosis and I have no doubt that it's correct," noted the physician. But the diagnosis also came with feelings of hopelessness. "It is very important that the family understand that sadly there currently are no treatments for this disease, in other words, even here at NIH there is no clinical treatment trial for reducing body myopathy," the physician stressed.

But the effective sentence of "no cure, no hope" from one of the most authoritative voices on RBM still did not deter Jian, who by then had signed on FivePlus to test an experimental gene therapy for an ultra-rare condition for which even the world's most prestigious research institute had no treatment options.

### RESEARCH SETBACK

Months after the November day when Jian came to FivePlus and signed the research agreement, the batch of RBM animals from UCSD arrived in China in March. After one month of quarantine and rounds of documents, the mice finally arrived at the company's lab.

According to a research paper published by the UCSD team, the rats need to reproduce to ensure sufficient numbers to perform studies, but in China there was nowhere to find suitable mates, so alternatives had to be found. Soon the number of RBM rats expanded to dozens, but strangely they did not develop the condition and die within a certain period as planned. Later research also confirmed the rats failed to develop RBM.

The unexpected results had researchers puzzled, so they started communicating with the UCSD team about the results but no real progress was made. The experimental work thus came to an abrupt halt in June. Seeing no path forward, FivePlus decided to end the project pending a new approach to salvage it. Facing a backlash, the Beijing company reconsidered its decision to tackle some ultra rare conditions, despite the early success with hereditary optic neuropathy.

For Yue's condition, his particular mutation has its challenges. There are distinct splice variants of FHL1, namely FHL1A, FHL1B and FHL1C and the boy's mutation was found to lie in between the variants.

### GENERAL CHALLENGES

More generally, gene therapy itself remains a complicated process. The eagerness to develop breakthrough technology and to be recognized as a global pioneer among many young Chinese researchers has also caused some concern over the speed and ethical practices involved in

gene therapy and editing research in the country.

Last November, Jiankui He, from the Shenzhen-based Nanfun Institute of Technology, shocked the world with an announcement of the birth of the world's first gene-edited babies. Amid a global outcry over the lack of sufficient ethical clearances and peer reviews, China significantly tightened oversight of gene research studies. (Also see "China Tightens Clinical Trial Oversight Post Gene-Edited Babies Scandal" - Pink Sheet, 28 Feb, 2019.)

Gene therapy is not simply a drug product but is more akin to a surgical process, noted Xiaobing Wu, founder of the FivePlus-associated Ruixi Gene Technology Research Institute. One of Ruixi's early backers included the mother of a young girl with Sanphilippo syndrome, and since then the institute has taken on spinal muscular atrophy and other rare neuromuscular conditions.

Many uncertainties still surround gene therapy as an emerging treatment modal-

ity, and researchers and patients must prepare for these.

### HOPE REMAINS FOR YUE

NIH researcher Bonnemann agreed that for RBM research further studies to gain a better understanding of the disease's mechanism may be the best way forward. "We are currently trying to understand the 'natural history' of the disease and investigate the MRI [magnetic resonance imaging] appearance of the disease, but again, sadly at this time we have no treatment to offer," noted the specialist.

However, Jian is refusing to throw in the towel just yet, and said he was in discussions with other researchers to find a new gene therapy to treat his son's condition. Despite the setbacks, being told there is no cure by a medical expert and facing large out-of-pocket expenses, the father said he had no regrets. His quest to find a cure for his son goes on.

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BRIAN YANG

## Fully Connected Data Infrastructure Offering Will Support Individualized Cancer Therapies

**A new digital ecosphere to support the efficient delivery of individualized cancer therapies to patients has been released by data and information management company EY. It is an open source framework that can be accessed by all stakeholders in the care delivery chain.**

As the delivery of medicines shifts towards outcomes and individualized patient care, the focus for service providers turns increasingly to how best to meet this demand for value with tailored solutions from systems that can be accessed by multiple stakeholders in the value chain.

Data management and compliance service provider EY has developed a connected data infrastructure system, Pointellis, which is initially addressed at cancer patients' therapies and needs. It is a delivery system that can make adjustments to patients' care based on need. The system, a cross-platform, open source framework built on Microsoft Azure, can be accessed by hospitals, labs, logistics centers and others in what EY is calling a "full digital ecosphere that

services parties involved in individualized cancer therapy."

Speaking to *In Vivo*, EY global life sciences digital, social and commercial innovation leader Adlai Goldberg said that the world of individual therapies was creating a very big change for health care and drug manufacturers. "The old world was a factory-to-patient model, but in the individualized world, it's a case of 'How do we take blood or tissue from a patient, bring it back into a manufacturing concept to make a product of one, and safely return and administer it to the same patient?'"

Health care and pharma are not set up to do that today. A few individualized therapies have been launched, but the pipeline volume and number of programs

on the horizon – at the last count, over 850 – is going to lead to a revolution in health care. "The question is how do we deliver, not to tens or hundreds of patients, but to hundreds of thousands of patients with different indications? That really is the challenge ahead."

New cancer cases per year are expected to reach 23 million by 2030, but a blanket approach to treatment will not produce the results that individualized care can. For the latter to work, operating models and supply chains must be put in place to improve how each therapy is designed, manufactured, delivered and administered to the right patient, consistently. Pointellis is EY's solution to those needs, as it helps create supply chains that are "as bespoke as the treatment itself, one for each and every cancer patient," said Goldberg.

"What we're seeing is that, to deliver that kind of care, there are many different organizations and systems that have to be

connected really well, to ensure a seamless and timely experience. Connecting them across unrelated entities is really the crux of the problem.” A few organizations are trying to solve supply chain or chain of custody challenges. However, the ecosystem of systems needs to be connected in some way. “We’re solving that data exchange issue.”

EY’s business model has been evolving and it is not a newcomer to bringing such data management solutions to the market. “Clients have requested it, because we’re good at managing data and information and data compliance, and providing protection around it.”

### PROVIDERS' CONCERNS

From a provider’s point of view, there is concern that each individual drug manufacturer will be approaching them with a different system to connect to. “Once we’ve built the system and provided access to it, it becomes a one-time installation, and many others can leverage it without having to replicate the level of connectivity that they would require.” There are already a few others in operation, but down the road, that number will grow. Still, they will want access and connectivity to the many different therapies that will be coming in three to 10 years’ time. The model could also include medtech, and cell and gene therapies, once the infrastructure is in place and ready to be developed.

The key advantage is that the system can swiftly and accurately manage demand in cancer therapy, by taking steps out of the chain. Pointellis’s core functions center around:

- biometric chain of identity and chain of custody, to track and trace biopsy tissue and blood samples from point of care when the patient first enters the system, all the way through medicine administration; and
- supply chain, to allow for enrolment, scheduling, demand and capacity planning, as well as coordination of logistics and delivery.

The system also enhances patient engagement, by sharing appropriate information. It does this, too, for oncologists and the health care providers treating critically ill patients, by offering decision support based on the wealth of



“These are early days for all of the individualized therapies, but it’s an exciting future”  
– Adlai Goldberg, EY

data captured through the platform.

Further, outcomes can be measured more accurately and allow providers, health systems, payers and manufacturers to adapt treatment and improve clinical benefit. The system also has payment management support tools.

One of the key challenges that individualized therapies are faced with is that there is a lot “human-ness” in this process: people might miss a blood appointment, or a package of blood tissue might get lost, etc. But in this new end-to-end process, users are more aware of where everything is, allowing for better demand planning. “Can we demonstrate improved capacity and predictability? That’s been our starting point for this information system.”

This was just the beginning, said Goldberg. “We are really only at Day One with these individualized therapies, and so far, only a few hundred patients have gone through this process. But we expect

that when it is really at scale, many application providers will be able to draw on the data and deliver better patient experiences.” Doctors will similarly make better decisions around treatments. These are early days for all of the individualized therapies, but it’s an exciting future, said the EY executive.

There are other, similar application providers in the market, but many struggle with access to data and getting the connectivity part done. As to the decision-makers regarding installing Pointellis, the various organizations are figuring out themselves how to automate services for greater efficiency and for individualized treatments.

It is a technology that is being developed in parallel to Blockchain. “Longer-term, we view Blockchain as the technology of choice to be able to do this, but right now, certain organizations are not quite at the level of maturity that Blockchain demands.”

At the end of the day, Pointellis will create an immutable record of the patient journey. “Our experience provides the safest way to manage their data. It provides only the relevant elements.” It also represents a way of reducing overall structure costs, meaning savings for the health care system.

Application providers will be able to build applications on top of it to leverage the data, either data-light or data-heavy applications.

“We’ve started with oncology, but the individualized nature of the technology spans much broader than just oncology.” Openness is fundamental and key to the design. “One of our biggest challenges is getting as much connectivity built as possible – and there’s only a short runway: the number of Phase III therapies is set to explode by 2021/22, so there is a real and immediate need to get this infrastructure in place.”

The system has been co-developed with key drug manufacturers. The aim is to ensure as many therapies as possible can be brought to patients on an individualized basis. “We will continue to evolve the platform,” said Goldberg. “Technology is never finished – it’s out there!”

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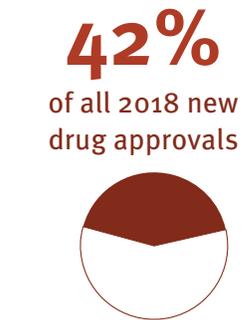
ASHLEY YEO



# PROGRESS IN PERSONALIZED MEDICINE

Industry's focus on treating the individual patient looks set to continue as more personalized drugs gain approval.

## FDA 2018



## 2018 HIGHLIGHTS

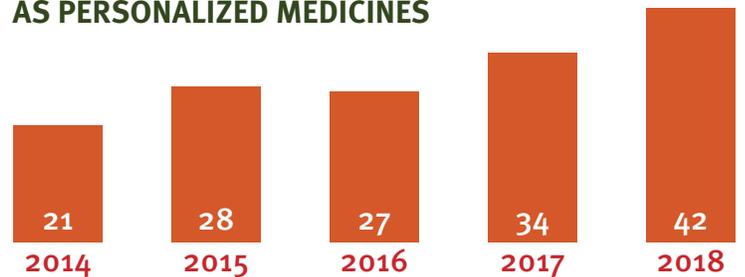
Approval of **Onpattro (patisiran)**, the first targeted RNA therapy



Approval of **Vitrakvi (larotrectinib)**, the 2nd cancer drug approved based on biomarker not tumor type



## PERCENTAGE OF US NEW DRUG APPROVALS CLASSIFIED AS PERSONALIZED MEDICINES



## Regulatory Evolution

**24**

of the 25 new personalized medicines approved in 2018, were subject to some form of expedited FDA Review

### Accelerated Approval Pathways:

- Orphan Drug Designation
- Priority Review
- Fast-track
- Breakthrough Therapy Programs



Two new biosimilars for existing personalized medicines were also approved in 2018:

**Truxima (rituximab-abbs)**, the first biosimilar to Rituxan

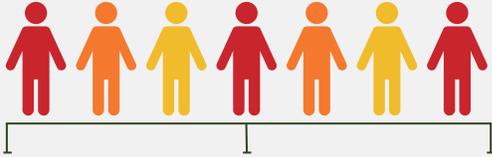
**Herzuma (trastuzumab-pkrb)**, as a biosimilar to Herceptin



SOURCES: In Vivo; Personalized Medicine Coalition; PhRMA

**MAKING A DIFFERENCE WITH PERSONALIZED TREATMENT**

**PATIENTS**



**THERAPY**



Without personalized therapy patients can have mixed results and some experience adverse effects with little benefit

**PATIENTS**



**BIOMARKER DIAGNOSTICS**



**THERAPY**

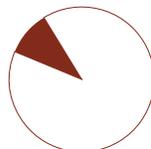


With personalized medicine each patient benefits from individualized treatment, which can lead to better results

**A Trend Set To Continue**

Technological advancements are providing the tools for better collection of individualized patient data. **More approvals for personalized therapies are expected**

**10 years ago, personalized medicines accounted for less than 10% of NMEs approved annually**



**25 PERSONALIZED MEDICINES APPROVED IN 2018 BY DISEASE AREA**

**BLOOD DISORDER**

**Doptelet**  
Dova Pharmaceuticals

**Mulpleta**  
Shionogi & Company

**GENETIC DISORDER**

**Symdeko**  
Vertex Pharmaceuticals

**Onpattro**  
Alnylam Pharmaceuticals

**Crysvita**  
Kyowa Hakko Kirin Co. Ltd.

**Galafold**  
Amicus Therapeutics

**Palynziq**  
BioMarin

**Takhzyro**  
Takeda Pharmaceutical

**IMMUNE DISORDER**

**Revcovi**  
Leadiant Biosciences, Inc.

**INFECTIOUS DISEASE**

**Biktarvy**  
Gilead Sciences

**Krintafel**  
GlaxoSmithKline

**Trogarzo**  
TaiMed Biologics

**Pifeltro**  
Merck & Co.

**ONCOLOGY**

**LutATHERA**  
Advanced Accelerator Applications

**Libtayo**  
Sanofi

**Mektovi**  
Array BioPharma

**Talzenna**  
Pfizer Inc.

**Braftovi**  
Array BioPharma

**Lorbrena**  
Pfizer Inc.

**Tibsovo**  
Agios Pharmaceuticals Inc.

**Vitakvi**  
Bayer

**Vizimpro**  
Pfizer Inc.

**Xospata**  
Astellas Pharma

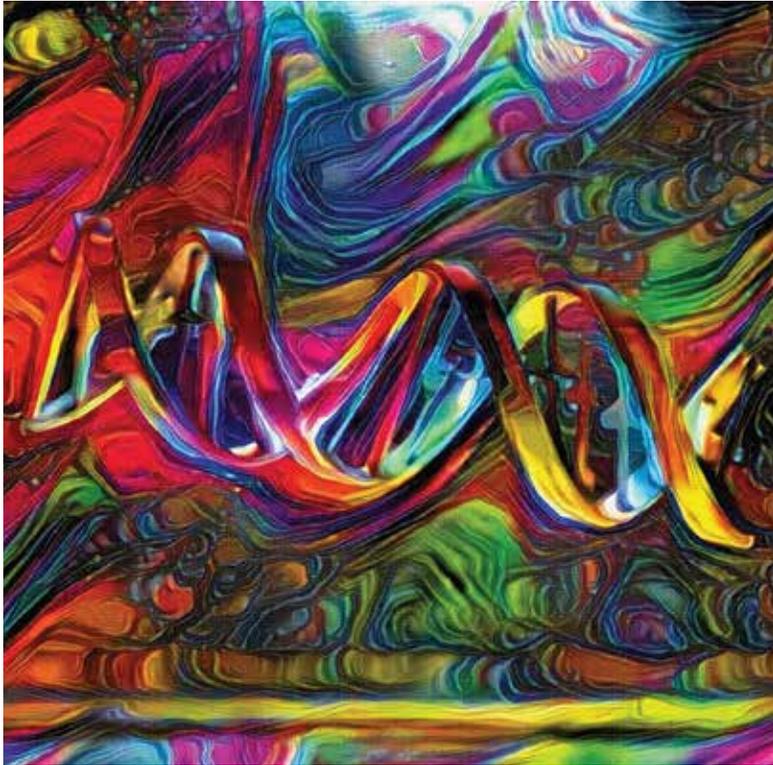
**RARE DISEASE**

**Tegsedi**  
Akcea Therapeutics

**Firdapse**  
Catalyst Pharmaceuticals

Credit: Gayle Rembold Furbert | Design | Pharma Intelligence

# Illumina CSO Paints A Vision For The Future Of Precision Medicine



Genomic medicine is coming of age. For Illumina chief scientific officer David Bentley, that not only means improved technology, accuracy and coverage of gene sequencing and a broadening into cancer, but also a better understanding among the wider population of disease and precisely the benefits that gene sequencing can bring to patients – actual and pre-symptomatic.

## BY ASHLEY YEO

Genomic medicine and genome sequencing are well-known technologies within a narrow, specialist audience, but the potential of the early diagnosis and targeted therapy information that they deliver remains substantially unknown among the very group of people whose lives they can change.

Illumina, the global driver of this UK-originated technology, is breaking boundaries and raising awareness of these crucial diagnostic tools, through initiatives like the 100,000 Genomes Project and the UK Biobank Vanguard initiative.

Nevertheless, Illumina is still learning where it sits in the industry and is driving to add to its capabilities, currently with a long-read target in its M&A sights.

Diseases could be detected even before people experience symptoms, thanks to a pioneering new health data program as part of the UK's modern Industrial Strategy. That was the message from the national government on July 23, as it announced a package of investment in Accelerating Detection of Disease, a new project to support research, prevention, early diagnosis and treatment for illnesses including cancer, dementia and heart disease in the UK.

The program promises to change the delivery of health care and medicine, building it around precision health care by making genomics central to early identification of disease. There is a longer-term aim to sequence 5 million genomes by 2023–2024, via a genomic volunteers program. This will improve the ability of health care professionals to tackle illnesses before symptoms occur. Program leader Professor Sir John Bell said being able to identify at-risk individuals with greater precision would have a profound impact on the development of diagnostics and new ways to treat disease. (Also see “UK Early Disease Detection Project To Use AI And Health Data” - *Medtech Insight*, 26 Jul, 2019.)

Music to the ears of David Bentley PhD, the CSO of San Diego, US-based **Illumina Inc.**, a UK life sciences colleague of Bell and someone who shares his conviction about the vital role of early diagnosis. “Unlocking the power of the genome” is Illumina’s particular mission, he explained to *In Vivo* at the group’s purpose-built EMEA headquarters in Cambridge. That, too, had been his mission at Solexa, the UK DNA sequencing firm set up in 1998 to conduct work initially at the Cambridge Department of Chemistry, before it secured a NASDAQ listing and, in 2007, was acquired by Illumina for \$650m.

Sequencing a whole human genome is a specialist endeavor, he said, “but it works

extremely well for us, as we bring human health, genomics and medicine together in one very important message.” Illumina is well known among the specialist audience, its systems having sequenced over 90% of the world’s sequenced DNA. More sites are adopting the technology to create an “ever-growing network.”

But where Illumina is a known brand in a narrow target market, the technology is hard to understand for the vast majority of people. “It’s a very big concept, but not very tangible,” Bentley acknowledged, which is evidently a barrier to broader acceptance and uptake. “People do need educating about the genome, so when we start to talk about it, we refer not to the genome, but to DNA, about which the public now has a pretty good idea.” That might be due in part to other, more tangible industries popularizing expressions such as, “It’s in our DNA,” thereby conveying the essence of the being – the genome – and the intimate role it plays in health and disease.

Illumina does not advertise its brand, and Bentley describes the company as “still very much in the finding-out game, and learning where we sit in the industry, what we do and don’t provide.” The company celebrates its 21st anniversary this year, which is young compared with big pharma. One of the many areas it wants to expand into is long-read technologies, and it is targeting that with the planned \$1.2bn acquisition of Pacific Biosciences of California Inc. (PacBio). The deal, which is at present being examined by the UK Competition and Markets Authority (CMA), but might yet be completed by the fourth quarter of this year.

“Whether long- or short-read technologies, scientifically, it’s very important to take the benefits back to the patient of whatever you can bring to bear on reading DNA,” said Bentley.

### Medicine Comes Earlier

One thing is sure for Bentley: “We’re totally committed to the core mission of human health. A key focus for us is enabling precision medicines development.” Getting the message over is the challenge, though he notes that people are suddenly very interested in their genome when they realize it can be a health benefit. The momentum increases in poi-



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*“People do need educating about the genome, so when we start to talk about it, we refer not to the genome, but to DNA, about which the public now has a pretty good idea.”*

– David Bentley

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gnant cases or when people in the public eye are being diagnosed in perhaps tricky cases. That they can have their genome sequenced brings to bear the power of the genome, and raises awareness of broader issues, such as the likelihood that every other person will suffer from cancer in some form – and may well benefit from genomic technology.

And there is a certain tailwind, as the perception of medicine changes, and society embraces a more generalized emphasis on wellness. The NHS is moving from treatment and management to prevention and early detection, which means individuals doing something when they’re healthy and well. “Genomics might have the capacity to predict what people might be suffering from,” Bentley said. Most medicine is still focused on treatment of people who are already sick. “We need to see if we can keep them well – getting their genome tested and treating them earlier.” And additionally, saving on hospital care costs.

### Still Too Hard To Understand?

The big question is: will people in general understand it, or will they be confused or misled by the whole field? It’s all down to education of the general public, who need to get to know it, understand it and become less fearful of it.

Whose job is that? It’s a shared role, of course, but Bentley’s view is that the media plays a huge role. NHS England chief medical officer Dame Sally Davies has had a huge, positive impact on medicine. She is getting the message across that the medical profession sometimes cannot determine a patient’s problem. But a genomic test can show that a person does not have cancer, for instance. Thus, the GP is instantly better informed, Bentley said, “To get rid of the fear, there has to be something to follow it up – something to change their outcome. People do understand and care about their own health, as we see in the rise in wearables; it just has to be clear information, presented in the right way.”

If genetic testing follows the trend of wearables, and becomes readily accessible, able to fill in all of the gaps, like phenotypes and medical indicators such as pulse and blood sugar – and can be done at any time in a person’s life – it

will likely become very popular. And when people realize it's just a simple blood test, they begin to lose their fears, and become empowered to ask about it. "That's where the whole thing starts to take off: when people start to want to know more in place of worrying about knowing less," Bentley said.

He added, "Getting tested won't condemn [people] to an unhealthy existence. The message is, it's a simple test. And if it does give them bad news, they can be taken on a journey and treated much earlier. It's still beneficial."

### **Illustrina's Major Ambition In Cancer**

One of Illustrina's major ambitions is in cancer, including in the study of the whole genome, where all the changes happen. "Let's look at [the DNA of] the whole cancer and at all the mutations," said Bentley. "Our ambition is to take a cancer and examine the whole genome, the complete panoply of mutations that has given rise to the cancer, read their profile with the signatures there in the DNA, and see how they have changed the DNA."

That allows a study of the mutations that are really driving the fast growth, puts the whole picture together and allows professionals to target a drug for the mutation that is essentially driving the cancer. That's a really important area for Illustrina: using the power of the whole genome, and getting "all the information out all in one go." It takes as little as two days to get the information out in individual cases, noted Bentley.

### **The Primordial Importance Of Early Detection**

Alongside the individual disease targets, Illustrina's overriding interest is in truly early detection and monitoring, which applies to the healthy and worried-well as much as to the symptomatic. It could be the same 10-minute blood test, and for the worried-well, it would be an instant result that would probably ease their fears.

Illustrina spun out Grail, a company it formed in 2016, that was deeply involved in pre-symptomatic cancer detection and was developing a routine blood test that is preventive and actionable. Grail uses Illustrina technology and the two companies have shared protocols. This field is now

### **A SIMPLE BLOOD DRAW TO UNLOCK GENOMIC COMPLEXITIES**

Genome testing can play a role at any time of life, Illustrina's David Bentley notes. The genome a person is born with changes in two ways: via epigenetic modifications when DNA gets modified as cells use the information in the genome differently; and by additional changes that happen after birth and in later life, that can lead to cancer. These changes can go on accelerating, following exposure to toxins, radiation or smoking, for example; and the side effects of drugs could increase mutations. So it is important to keep monitoring it. The beauty is it needs just a blood sample to find the cancer and know if it is developing or changing. "You can't prevent cancer, but you can cure it, and much more effectively if the cancer is caught early, when it is at a low level."

getting very big and Grail is now also working with NHS. But there has been a rise in local clinical organizations wanting to do the early cancer detection themselves, and Illustrina is getting more involved in helping promote and provide genomic technologies that are suited to the task.

### **Partnerships**

These illustrate one type of partnership that Illustrina is pursuing to take it to its next development stage. The challenge of finding a trace amount of cancer in a blood test is very different from looking at the entire spectrum of mutations in one individual, Bentley points out. They are quite complementary approaches, but not yet honed to routine medical practice. "That's where the partnerships with the NHS, US health providers, other local research and translational medicine organizations are very valuable to us. They teach us what we should be building."

Such partnerships also show Illustrina what not to concentrate on. "For us, it started with DNA sequencing and genotyping. DNA technologies are our

bread and butter, and we continue to innovate hugely there, but the question is: how much more do we do?" Illustrina sometimes builds, sometimes partners, sometimes acquires, said Bentley. "Sometimes we leave well alone, as in the case of health records – not our forte."

### **The Days Before Sequencing**

Before sequencing technology was developed, clinical geneticists would perhaps diagnose 5% of cases presented to them. In a controlled genetic study run by Illustrina for underserved families in Mexico, the "iHope project," the diagnosis rate reached 68%. Almost half of those diagnosed (49%) had a resulting change in disease management. "That surprised us, but it showed what could be done," said Bentley. "That's the impact of what we have today with Illustrina," but he added that the other 30% is still there. "What are we missing? We can always find more mutations, diagnose more children, diagnose them earlier, before they get sick, and prevent, rather than having to cure, and in rare genetic diseases especially. So we can always do better."

He continued, "If we went right to very early stage, finding a genetic disease before it becomes serious, we'd raise questions on social and ethical levels about just how early you want to go with testing. Do people actually want to know?" They certainly would want to know that when they were already sick, or if a family member had died from the disease, Bentley said, but to go further would require people to have a greater understanding of the technology and its purpose.

A classic example is seen in Huntington's disease, for which an experimental treatment some 18 months ago from University College London (UCL) showed promising results. Before that, the ethical dilemma was whether to tell the patient he or she had the disease. But once a treatment is available, it will change how the genomic information can be used. People now more readily say: "I want to know now, and get enrolled for early treatment," now that the treatment and the diagnosis are very much hand in hand.

### **Pharma's Role**

"If you really want to prevent disease, you have to [be able to] test people who are well. Otherwise, prevention won't

happen. In that sense, we can do better for patients and hopefully save health care providers money at the same time, by keeping people out of the hospital, or getting them home quicker.” The pharma industry would be able to develop the right medicines to target patients much more quickly, using both existing and new medicines.

“This is a whole research and discovery opportunity that requires many years of very close partnership with genomic technology companies, health care professionals, patients, and with pharma.” Genomic medicine is the essence of precision medicine, the essence of the future, and of being able to tailor medicines and other treatments. It spares cases where surgery would have been recommended, and thus can save on expensive treatments that would not have done any good.

“As for Illumina, we’re more about the technology that leads to the early diagnosis and not about developing the treatment that needs to follow. But we do see ourselves as working hand in hand with companies that are developing those treatments,” said Bentley. “They can revolutionize our space, and we can revolutionize theirs as well. We can tell these companies which treatment will work and in which patient, and in those patients where it will not.”

In almost every disease, there is a genetic component. “If we together had all the imaging data, analysis and outcomes, and then looked at the genomics of those individuals, you would soon begin to predict disease long before there are any symptoms,” he stated. That would enable them to be fast-tracked to something that will improve their outcome. It is the idea behind Illumina’s concept of focusing on technology to address rare and undiagnosed genetic diseases, which affect an estimated 350 million people worldwide, half of whom are children.

### The Language Of Partnering

There are many ways to secure needs via the networking element of partnering, Bentley explained. “I have always focused on individual doctors and clinical geneticists, right up to organizations, thought leaders and the NHS. I wanted to understand the problems they were

facing, not simply to go on sequencing more and more DNA.” That’s all very well, but does it cure the patient? Building partnerships means speaking different languages and addressing different priorities. “We gain a huge amount of strength from these partnerships.”

But again, he stressed the need to do more. Bentley recalls that Illumina’s work on genomes with the NHS started with a single conversation with one doctor, Professor Anna Schuh, who was interested in genomics, but needed support. She became one of the key influencers in the UK, long before Genomics England had started, and is now head of the blood cancer clinical interpretation partnership group for that organization. Chris Wigley, Genomics England’s new CEO designate, will assume his role on October 1.

With Professor Bell, Professor Peter Donnelly and others, Schuh helped start the 500 Genomes Project – led by Professor Jenny Taylor – in 2008, the very first major complete genome sequencing project in a health care context, in collaboration with Illumina. That opened

### THE ENGLISH LEGACY AT ILLUMINA

Bentley came to Illumina legacy company Solexa from The Wellcome Sanger Institute, having helped found the company in 1998. In the ensuing eight years, Solexa developed sequencing technology, in 2005 having sequenced the complete genome of bacteriophage phiX-174. Solexa acquired California company Lynx Therapeutics, and secured a NASDAQ listing, but the underlying proprietary chemistry came out of the Cambridge Chemistry Department, DNA sequencing having originated at Cambridge. Bentley was Solexa’s chief scientist in the two years before Illumina acquired it and has continued as Illumina’s chief scientist for San Diego, US-based Illumina, living in England. Frances de Souza is the current CEO.

the door, allowing thought leaders to see what could be done. Davies then spearheaded the 100,000 Genomes Project, dependent both on Illumina providing the technology to match the needs, and on Genomics England being formed to bring together elements of the NHS to build an infrastructure that reached out to genetics centers across the UK.

“That was something that had never been done before. It was a true partnership, but very challenging,” said Bentley. “Everyone had to put aside their individual interests and think to the future. In that sense it was just like the Human Genome Project all over again.” The HGP (1990–2003) was heralded as the biggest example of open collaboration. An international meeting in Bermuda led to the drafting of the Bermuda Principles of data sharing. “We had to put aside our more local and regional projects. We wanted to give the data to the whole world for free.” It was a very important driver of international collaboration, stated Bentley, and although one or two countries had to pull out, those that stayed the course got up a head of steam, all wanting to contribute.

Bentley had been consulted on whether it was possible to build on the 500 Genomes Project to do the 100,000 Genomes Project. He had talked with Bell about the 500 Genomes Project initially, and Bell’s support gave it much credibility. The first initiative reaped a 30% diagnostic yield.

The 100,000 Genomes Project took a leaf out of the HGP with its focus on sharing. Illumina has taken those principles on board too. “Many companies want to become data companies, but we’re not committed to that. We generate data, but we don’t hold it; we delete the data as soon as it has been recognized as having been delivered to Genomics England.”

The company does some interpretation (as in the iHope project), but doesn’t keep the results. “We release anything we find into the public domain, and by doing that, it opens the door to partnerships.” Bentley said that after Illumina had submitted some of its data to US databases (ClinVar and ClinGen), it was invited to be part of their organizations. “We will all gain from what we want to share with each other. It’s a wonderful dynamic to get into.”

## Relishing The Freedom To Operate At Illumina

From single partnerships right up to the grand scale collaborations, Bentley has had a certain freedom to bring his expertise to bear at Illumina. “Personally, I’ve always wanted to go for the biggest problems, and Illumina has allowed me to do that.”

It’s hard work at Illumina, he confided, “but you can leap out into a longer-term picture, paint that picture at Illumina, and offer a glimpse of what the world will look like in 10 years’ time.”

But he is mindful to be very focused on how both Illumina and the wider world will benefit. “I always choose the long-term option; if you can do a whole genome, you can do part of a genome. But if you try to do part of a genome you won’t know if you can do a whole genome. That was the big one for me: I always concentrated on the whole genome,” he reiterated.

## Uncharted Territories And Potential Sensitivities

A child with an undiagnosed disease usually ends up in intensive care. Most serious diseases manifest themselves early – anytime from the dawn of life, and typically at the age of five. Right at birth, the child might have a rare disease, some of which go undiagnosed after repeated tests and many well-intentioned but misguided treatments or operations. Illumina describes this period of searching for answers as the diagnostic odyssey. In many cases, the genome data, however, provide the key. The data give a view of the whole genome, and could circumvent wrong diagnoses and unnecessary operations, saving both money and resources, and giving a more normal life to the child if there is a treatment to follow the diagnosis.

Without the help of genomic data, by the time of a successful diagnosis, it’s often too late to have a truly positive effect. Early diagnosis is particularly important in neurological diseases, such as epilepsy. That information permits a correct intervention, and prevents the child later having to come into the ICU. But it’s an issue for careful consideration. Would the parents want to know? This was an unresolved question, Bentley said.

Older children with a genetic disease are now being offered sequencing as mainstream care in the NHS. That was one of the

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*“We see ourselves as working hand in hand with companies that are developing treatments – they can revolutionize our space, and we can revolutionize theirs as well.”*

– David Bentley

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missions of the 100,000 Genomes Project, which was completed in 2018. Professor Sue Hill, who led NHS England’s contribution to the project, said England had become the first country to offer equitable access to the technology across its entire population. Bentley stresses that all 55 million or so of the population did not need to be sequenced, but that the point was everybody can get access to the same test. “It was a huge step forward, and we’d allayed fears, showed the diagnostic benefit.”

Bentley thinks the inflexion point has been reached: if the 100,000 genomes was the “soundbite,” the next 1 million is already in the planning. “It’s not an aspirational target; we will do a million in a few years, and on Illumina technology.” Other technologies will be used as well, but Bentley adds: “We’ve done enough to show that this is the best way today to do genomes.” On the other hand, the 5 million genomes, which the Office for Life Sciences (OLS) and NHS England were

involved in planning, is an aspirational goal, and is “much bigger than Illumina.”

## Next On The List For Illumina

Although Bentley agrees that people need to know more about Illumina and its role in early diagnosis and disease prevention, he asserts that it should only be for the purposes of accelerating uptake of whole genome sequencing in medicine. He wants national organizations outside the UK to be aware of whom they should approach, and that Illumina can offer partnerships. Many key organizations already use Illumina technology, such as 23andMe and Grail, for example.

“We’ve been in this space for a very long time,” Bentley said, and “the confluence of precision medicine, pharma and biotech has led to the dawning realization that precision medicine is achievable, and no longer a future dream.”

For Bentley, genomic medicine is truly coming of age. The opportunities lie ahead for an ever-better reading and understanding of the genome, and improving technology, accuracy and coverage. Rare disease was where genomic medicine started, but Illumina is now moving into cancer, which is a much bigger and more complicated field, and genomics will gradually change the understanding of the disease. Other diseases will be tackled in time. “Genetics helps diabetes and heart disease, and we’re beginning to look at projects on sudden cardiac death and neurological diseases, given that some of the risk factors are genetic,” he said. “Understanding the molecular mechanism of disease with the help of the genome part highlights what’s gone wrong, and thus the bit you want pharma to work on.”

This is only possible because Illumina pushed ahead with innovations. “We innovate massively, investing more than any other medtech company in this space,” he noted. Illumina contributes 18% of its expenditure into R&D. “That’s what will unlock the power of the genome. It’s all to play for, and – we’re still just at the very beginning,” said Bentley. “My job is to paint the vision, and the main thing for us is to continue to partner, and collaborate. That focuses our innovation.”

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### Comments:

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# Rgenix: A Cancer Start-Up's Resolve To Crack The Mystery Of Metastasis



MASOUD TAVAZOIE, RGENIX CEO

Rgenix, a New York-based start-up co-founded by three prominent physician researchers, is taking aim at what it contends is the future of cancer treatment: finding drugs that shut off the biological chain reaction called tumor metastasis – the colonization of malignant cells throughout the body that ends up killing the majority of cancer patients.

## BY WILLIAM LOONEY

The company has a strong IP portfolio rooted in its founders' ties to Rockefeller and Columbia universities, with three investigational drug candidates now moving forward into clinical trials.

Rgenix's lead compound, RGX-104, is an oral small molecule LXR agonist that targets the ApoE gene to regulate cancer progression. A Phase Ib/II trial for an indication in lung cancer is beginning patient enrollment; RGX-104 also carries FDA orphan drug designation for three other tumor types.

The company has numerous ideas on potential partnering tie-ups to help drive its platform toward commercialization. Its position is grounded in the financial reality of the \$100,000 plus per patient cost of clinical trials to drive its candidates forward.

In the fight against the seemingly random pathogenesis of cancer, one standout innovation is the ability to suppress the actions of specific genes that drive tumor progression in different cancers – the dreaded metastatic phase in which the spread to other organs makes the disease a uniquely prolific killer. It is an unmet medical need of the highest order, yet most cancer research today centers on a rearguard mobilization of the immune system to find and destroy cancer receptors in individual tumors rather than address the underlying drivers of cancer growth and dispersion, across different malignancies. Yes, killing cancer cells in the tumor represents a step forward, but from the expectant eyes of the patient the ultimate test is death by metastatic disease – so shouldn't preventing that lead the future of cancer research?

Three entrepreneurs determined to answer this question are Masoud, Sohail and Saeed Tavazoie, the sons of immigrants from Iran with complementary backgrounds in cancer care and academic research. Sohail, a medical oncologist and cancer biologist, and Saeed, a systems biologist, run their own academic labs at Rockefeller and Columbia universities in New York, respectively; Masoud, also a physician scientist, trained as a clinical dermatologist.

In 2010, the three founded a private start-up, Rgenix Inc., to commercialize a cancer discovery platform based largely on their own research, with Masoud eventually taking the role of CEO. The aim of Rgenix is to develop novel small molecule and antibody therapies to slow or eliminate disease progression in cancer patients for which there are limited or no alternative treatments. It has taken nearly a decade, but the company is finally advancing to clinical trials with several compounds that will hopefully prove its thesis that finding and destroying the cancer cells responsible for initiating and promoting metastatic progression can be performed by a drug –

one able to short-circuit this biological chain reaction and extend patient lives.

### Bench – And Bedside – Perspective

The three co-founders are motivated by what they have observed in clinical practice. Cancer is always one step ahead of science, which means that physicians have many patients for which there are no effective treatments. Thus, the simple premise of the new business was to invest in new approaches that might offer more hope. “As a physician I trained in oncology and was discouraged by seeing so many patients with metastatic disease die without much benefit from traditional therapies,” said Sohail Tavazoie in an interview with *In Vivo*. “I continue to see that today despite the revolutionary progress cancer immunology has made in subsets of cancer like melanoma and NSCLC. That’s what led us to the biology of metastasis – the therapeutic rationale behind Rgenix is finding in each cancer type the key gene that drives its progression in individual tumors and growth to other organs.”

In contrast to the standard discovery route of sequencing cancer DNA to find mutations that drive malignancies, which is constrained by the fact that many patient’s tumors do not have identifiable DNA mutations that are druggable, Rgenix’s platform focuses on RNA and the proteins it regulates. RNA is now known to be more revealing than DNA in predicting the course of the disease. Specifically, the platform targets the non-coding micro-RNA that impacts the gene expression of so-called messenger RNAs (mRNAs) and the proteins that regulate cancer behavior, and, by extension, key aspects of that behavior such as invasion/metastasis, angiogenesis, and immune evasion. The approach conforms to the recent consensus among researchers that proteins are the physics of cancer biology, revealing vital insights on disease progression: how malignant cells activate, grow, spread, slow or stop, all in real time. Hence the Rgenix platform does not seek to develop drugs to modulate RNA itself but instead zeros in on the proteins whose normal expression has been “deregulated” – made cancerous – through the pathogenic signaling

of altered micro-RNAs. It is an important distinction, because disarming proteins that act as a cancer’s messenger can be done with high efficacy using a small molecule or antibody instead of a complex, autologous gene-based therapy.

### Do Cancers Have A Favorite Gene?

Tavazoie explains further the step-by-step process that guides Rgenix’s discovery platform. “Through systematic mapping of the micro-RNA landscape, we have discovered critical genes and proteins that exert extremely large effects on cancer progression. We then employ genetic, molecular, biochemical, pharmacologic and clinical association approaches to characterize the mechanism of action of the specific target protein. Next, we develop conventional small molecule and antibody therapeutics to engage the target and to move them forward as first-in-class cancer-fighting agents, all focused on those aggressive cancer cells that colonize different organs and will eventually kill you. From a clinical perspective, the target genes we have identified exert robust regulation of cancer progression across multiple pathologic processes, ranging from the phenomenon of innate immune suppression to angiogenesis in the tumor micro-environment.”

It may be too much of a simplification, but, as Masoud Tavazoie explains it, the method is disarmingly tumor agnostic. “We just tell the cancer to show us its favorite gene and confirm that with animal assays and then human tissue samples, after which we test a conventional small molecule or antibody drug against the protein target. In most cases, the drug target drives cancer progression using a mechanism that has a broad impact against an array of different cancers by, for example, suppressing the innate immune system. The premise is we learn to make the connections across cancers as we go along, with patient impact at the late-stage as our compass.”

As Rgenix CEO, Masoud has the task of communicating the company’s mission succinctly to investors, which now include blue chip names like Europe’s Sofinnova Partners, Novo Ventures, Alexandria Venture Investments, WuXi App Tec, and the Partnership Fund for New

## RGENIX’S ROLL CALL ON PRECISION MEDICINE

Cancer is a collection of diseases and symptoms that express differently in individual patients – thus all of Rgenix’s clinical programs have a “precision medicine” component, a characteristic reinforced due to the unique target discovery approach used across these programs. Here are three examples covering each of the company’s three compounds currently in development:

- Rgenix’s candidate RGX-202 to suppress gastrointestinal tumor growth has a precision diagnostic strategy already incorporated into its clinical development. The FDA has lent its support to Rgenix’s use of Creatine Kinase Brain-Type (CKB) to enrich for patients that, based on pre-clinical data, are more likely to respond in a Phase Ib expansion arm of its current trial in metastatic colorectal cancer.
- Rgenix is evaluating several potential companion diagnostic markers (cellular, protein and genetic) in the target pathway of its lead candidate compound RGX-104, which is being evaluated with the LXR/ApoE gene in suppressing immune response in a variety of cancers, starting with lung cancer. After the Phase Ib/2 data read out at the end of next year, the company will consider incorporating them to enrich for patients more likely to respond in subsequent Phase II/III clinical trials with RGX-104.
- The third pipeline candidate, RGX-019, a monoclonal antibody addressing tumor growth and immune evasion in several tumor types, including triple negative breast cancer, has shown in pre-clinical studies to have greater efficacy against tumor cells with higher levels of MerTK gene expression. Rgenix researchers plan to use a similar companion diagnostic approach for that program once it is in the clinic, likely in 2021, and potentially with a big pharma partner.

York City. For that, he channels his experience in treating patients. “As a clinician you have to step back and ask yourself what the patient wants, and the answer in every case is – a cure for their cancer. To do that, you start by asking what these patients end up dying from right now. The answer is metastatic disease. So our mission is to prevent what drives that process. It’s the future of cancer, where we can apply RNA biology and human genetics to identify not just patients at risk for cancer, but more precisely those facing the biggest risk of cancer mortality, with a higher probability of metastatic progression because of the genes they were born with or the genes that get deregulated in their tumors.”

One gene that has attracted the company’s attention is apolipoprotein E (ApoE), the deregulation of which has been implicated in tumorigenesis and progression, particularly for cancers of the breast and melanoma. “ApoE was among the earliest genes where researchers were able to show how its deregulation resulted in dyslipidemia, a process for which statin drugs were developed, and which are now very effective in reversing this condition,” Sohail Tavazoie tells *In Vivo*. “I believe this process is where the potential is in cancer as well, by uncovering those germ line genetic alterations that can predict metastatic relapse in individual patients further down the line.”

Tavazoie notes that Rgenix has produced preliminary evidence confirming in human studies that forms of ApoE can either inhibit or promote the likelihood of metastasis in patients with melanoma. For example, one inherited allele (sub-type) of ApoE, present in about one-quarter of the human population, is protective for melanoma metastasis; while another form, present in about 15 per cent of humans, is destructive and promotes metastasis. “The challenge is finding which variant the patient is genetically pre-disposed to and then create a drug that can put the brakes on that biology, perhaps in combination with medicines already approved and known to activate the standard T-cell immune response.” He says what matters most is developing agents that by themselves will significantly modulate tumor growth – the foundation of the Rgenix platform.

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*“Our mission is to prevent what drives the metastatic phase of disease. It’s the future of cancer, where we can apply RNA biology and human genetics to identify not just patients at risk for cancer, but more precisely those facing the biggest risk of cancer mortality, with a higher probability of metastatic progression because of the genes they were born with or the genes that get deregulated in their tumors.”*

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### Pipeline Prospects: The Gang Of Three

Rgenix has seeded its pipeline with three key assets. RGX-104, the first, and most advanced, is an oral small molecule liver X receptor (LXR) agonist that targets the ApoE gene and is in development for the treatment of solid tumors. The initial focus for clinical development is in lung cancer although the company has obtained an orphan drug designation from the FDA in three additional indications: malignant melanoma stages IIB-IV, glioblastoma multiforme, and ovarian cancer.

In a Phase Ia dose escalation study completed and presented at the American Society of Clinical Oncology (ASCO) last year, RGX-104 demonstrated an overall favorable safety profile with evidence of innate immune stimulatory effect and anti-tumor activity, as a single agent. Adds Masoud Tavazoie, “We are positioning this as a first-in-class medicine, in combination with other agents, that highlight our therapeutic focus on major areas of unmet need. In our view, RGX-104 is the most advanced LXR agonist coming out of discovery to date. It’s also the only LXR agonist we know of that’s in clinical testing for cancer indications.”

The next step for RGX-104 is the imminent launch of a Phase Ib/II trial that will test the compound in combination with other agents in lung cancer indications. RGX-104 will be tested in combination with standard of care chemotherapy and the checkpoint inhibitor Keytruda (pembrolizumab) in first line non-small cell lung cancer (NSCLC) patients whose tumors lack expression of the PD-L1 protein, which is an area of high unmet need in the first-line therapy setting. RGX-104 will also be tested in patients with a particularly aggressive form of lung cancer – small cell lung cancer (SCLC) -- in combination with the chemotherapy drug docetaxel in the second-line setting. “We are seeking to demonstrate our unique mechanism of action works in combination with chemotherapy and checkpoint inhibitors in those patient subsets in lung malignancies that have not benefited, or benefited a small degree, from such combinations. The goal is to boost that benefit and thus slow or prevent the inevitable progression of metastatic disease and

death,” Tavazoie told *In Vivo*. “In fact, from the early data, it appears the benefit goes beyond stimulating an immune response to suppress angiogenesis and prevent metastasis progression.” Rgenix has selected 17 trial sites for the RGX-104 Phase Ib study, with an estimated date for completion of patient enrollment in the second half of 2020.

The second asset, RGX-202, is another small molecule that the company is positioning for treatment of colon and other gastrointestinal cancers. Animal studies drawing on the Rgenix micro-RNA discovery platform have shown how the molecule creatine has a metabolic effect that accentuates survival of cancerous cells originating in the colon and rectum and helps them colonize in the liver, allowing these cancers to form metastases throughout the body. The investigational compound prevents cancer cells from taking up creatine, inducing in turn apoptosis (cell death) of metastatic cells in these animal studies.

At present, a Phase Ia monotherapy with dose escalation trial with RGX-202 is nearing completion. The plan is to start recruiting patients at seven US centers for a Phase Ib (RGX-202-001) trial in combination with the chemotherapy drug regimen FOLFIRI later this year, in patients with colorectal and gastric/gastroesophageal cancer. Interim data from the colorectal cohort is projected for the second half of 2021. “In many sub-sets of patients with colon cancer, such as those with KRAS-mutant tumors, there aren’t any approved targeted therapeutic agents that broadly target such tumors because it’s been difficult to identify druggable targets. We have uncovered a key pathway that represents an attractive small molecule target, not only in the colorectal indication but perhaps extending to other gastric malignancies and pancreatic cancer as well. It’s another example of our mission of creating new options for patients using our powerful target-discovery platform,” said Masoud Tavazoie.

The third asset in play, RGX-019, is a pre-clinical candidate, a monoclonal antibody that targets the MerTK gene, which Sohail Tavazoie’s lab at Rockefeller University originally identified as the trigger of tumor growth in triple negative breast cancer. It is now licensed exclusively to

Rgenix. According to Sohail, “MerTK is a very interesting kinase which is expressed not only on cancer cells, but also on the immunosuppressive tumor cell that block the body’s innate and adaptive immune response. Hence, RGX-019 targets both cancer cell proliferation and the immune response against tumors.”

The company has initiated the enabling work to support an FDA IND application on the compound by 2021. Because the MerTK gene is associated with the onset of a wide variety of cancers beyond breast cancer, including hematological cancers, progress on RGX-19 represents another area where Rgenix believes it can serve cancer patients whose individual conditions are not helped by current standard of care. However, on a competitive note, the oncologic effects of the MerTK gene has attracted significant interest among industry researchers. According to Informa’s Biomedtracker service, five other companies – Ono Pharmaceuticals, ElsayLs Biotech, Incyte Corp., Celldex Therapeutics, and AbbVie Inc., are involved in pre-clinical work on solid tumors; Ono also has a pre-clinical program for acute myelogenous leukemia (AML). Most of these compounds are small molecules, but Rgenix is employing an antibody approach that it believes will be best-in-class, given the antibody’s specificity for MerTK and its ability to induce MerTK receptor degradation – a unique mechanism of action compared to these other approaches.

### IP Gravy From GSK

As a counter to the intensity of industry activity in cancer, Rgenix relies on a solid portfolio of IP, starting with its close ties to Rockefeller University, exemplified by the more than two dozen researchers working with Sohail Tavazoie in his dual role as head of the University’s Meyer Laboratory of Systems Cancer Biology and the Black Family Center for Metastasis Research. The company’s three pipeline candidates are derived from basic research conducted at the Tavazoie lab over the past decade. RGX-019, which focuses on MerTK gene expression and remains an attractive target for many other industry players, is patented around original animal study research that Tavazoie first published in 2010, long

predating these other efforts.

“Rgenix has the credibility that many start-ups lack because it is grounded in a set of core principles around cancer progression and a powerful platform technology invented independently, in the academic setting. It is what attracted me to leave the venture capital field and join the company as its first outside employee,” said Rgenix chief operating officer, David Darst, in an interview with *In Vivo*. He also noted how Rockefeller helped jump start formation of the start-up by offering the three co-founders a license covering a full suite of IP protecting the micro-RNA protein technology, contingent on their raising at least \$2.5m, which was secured in 2013. A multi-year collaborative research agreement between Rgenix and the University allowed for amendments to the licensing package – eight to date – covering the three development programs’ pathways and targets as well as companion diagnostics that allow therapies to be personalized to the patient’s own disease profile (*see Rgenix’s Roll Call on Precision Medicine*).

“Overall, it’s a very close relationship,” said Darst. “In 2018 we moved toward a standard material transfer agreement (MTA) model as the University seeks more oversight of companies that interact with campus research. But we continue to work closely with Rockefeller’s technology transfer office. There is substantial institutional funding covering genetics and proteomics for cancer that will no doubt prove useful to us further down the line.” Nevertheless, ties between the two have matured. The platform has been brought in-house and the organic drug discovery engine is now led by Rgenix’s VP of R&D, Isabel Kurth, who is building a team of biochemists, computational biologists, and downstream drug development managers.

Not all of Rgenix’s technology originated in academia. Perhaps the company’s most ambitious move was the licensing in 2013 of the chemistry behind an LXR agonist developed at GlaxoSmithKline PLC and intended to treat atherosclerosis before it was shelved for increasing lipids in the blood. According to Darst, “we found that the drug activates our transcription factor and turns on ApoE, the gene we are most interested in for the

effects we were seeking in our lead candidate, RGX-104, initially for lung cancer. It took about 10 months of negotiation, including GSK rejecting our first bid. In the end, Rgenix secured a favorable license, mainly because the deal legitimized our business model for RGX-104. We realized there was strong IP out there that could be licensed around a lead program from a major industry player like GSK.”

### Open To Playing Outside

Along with expanding its IP portfolio, Rgenix has raised a series of four equity funding rounds, beginning in 2013 and most recently in September last year, when a series C placement pulled in \$40m with Lepu Medical, a China-based medtech firm, in the lead. Lepu has no strategic rights to any Rgenix program, in total, the company has raised over \$80m to date, including an initial \$2.5m in seed money raised to trigger the license rights from Rockefeller University

According to Darst, roughly \$50m has been spent so far, which leaves the company with about \$30m in cash on hand to finance the transition into full-scale clinical trial work. “We have three novel targets along with a small team of about 20 full-time staff committed to advancing these candidates to FDA approval as quickly as possible,” Darst said. “Even with reliance on dozens of outside consultants who we can draw on virtually rather than bringing them on full-time, it will be a challenge to expand in our base in New York City. A single patient in one of our clinical trials is for us a \$100,000 plus investment, which explains why the average cost for an approved drug ranges from a low of \$300m to as much as \$1.4bn. Our approach to partnering is grounded in this reality.”

Darst tells *In Vivo* that as Rgenix transitions to Phase II and III for its lead and two secondary programs, it will be “definitely open” to working with other biopharma companies to secure FDA NDA approvals, generate more novel research targets, push work on the MerTK program into additional indications, and consider support to secure eventual approval for the lead molecule RGX-104 in foreign markets such as China, Japan and the EU. CEO Masoud Tavazoie adds that while to date Rgenix has been successful by pur-

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*“Our strong clinical data combined with our first-in-class compounds will determine if and how we raise more money, go public with an IPO, dialogue productively with regulators and attract partners. We intend to be very judicious in applying this tool to support the growth of our business.”*

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suing its clinical program independently, on its own, future progress may demand a different set of drivers; thus, the key criteria required of any potential partner is “strategic fit.” One area of interest is helping the company accumulate, evaluate and leverage data. “Our strong clinical data combined with our first-in-class compounds will determine if and how we raise more money, go public with an IPO, dialogue productively with regulators and attract partners. We intend to be very judicious in applying this tool to support the growth of our business.”

### Future Forward

What comes next for Rgenix? Masoud said, “We have a lead first-in-class candidate that has demonstrated anti-tumor activity in patients, establishing proof-of-concept and proof-of-mechanism in a manner that, to us, shows our platform works. Now what needs to be done is to implement our clinical development plan, testing RGX-104 in those cancer patients most likely to benefit, leading eventually to an FDA approval in clinical settings of high unmet need with large commercial impact. That is the final bridge we must cross. And as we have put in place a strong clinical team, I am confident Rgenix will have at least one marketed product within the next four or five years.”

Sohail added, “It may seem a long journey, but getting clinical responses from a novel agent in patients at an advanced stage of disease, doing it all in six years from the start-up of operations, is a matter of personal and professional pride to me. That’s particularly true because, as a researcher who continues to see patients with cancer, I know how so many of them have limited time left. Rgenix is going to keep moving forward to extend that time – with approvals and therapies that provide meaningful clinical benefit to patients.”

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### Comments:

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# What Does It Take To Launch And Lead An Oncology Biotech Today?



CHARLOTTE CASEBOURNE, THEOLYTICS CEO

Oncolytic virus company Theolytics has emerged ready to raise a Series A round and get its preclinical assets into human trials by 2021. CEO Charlotte Casebourne talks to *In Vivo* about the challenge of standing out from the crowd in oncology, how viruses have evolved as a treatment approach in cancer, and how oncolytic viruses might be able to answer the cancer drug pricing conundrum.

## BY LUCIE ELLIS

Founded in 2017, Theolytics is a preclinical-stage biotech using oncolytic viruses to combat cancer. The Oxford, UK-based company is pioneering a “Darwinian” selection approach that leverages the fact that – by their very nature – the fittest viruses in a pool will out-compete when exposed to a given niche.

As the company comes out of “stealth mode,” CEO Charlotte Casebourne talks to *In Vivo* about its platform technology, the importance of differentiating its pipeline as a new biotech on the scene, and the skills required for a biotech leader today.

She also discusses the concerning issue of access, as novel personalized cancer treatments are reaching “eye-watering” prices on the market.

To date the oncolytic virus field has focussed on the slow, careful design of therapeutic viruses – an approach dependent on the human mind creating the best possible virus from thousands of base pairs. However, Theolytics is leveraging a convergence of emerging technologies within the viral therapy field – long-read sequencing, sophisticated bioinformatics and advanced genetic engineering – to accelerate discovery and development.

The company launched with £2.5m in seed investment from Oxford Sciences Innovation (OSI), a £600m fund focused on commercializing ideas originating from the University of Oxford. Lansdowne Partners, Wellcome Trust, Invesco, Google Ventures and IP Group – as well as sovereign wealth investors – are among OSI’s shareholders.

The company is now preparing to raise further funds through a Series A financing round. And later this year, it expects to announce the selection of a lead virus, as well as the target cancers that will be an initial focus for clinical trials.

In an exclusive interview, Casebourne speaks to *In Vivo* about Theolytics’ approach and the big issue of differentiation that faces all companies entering the oncology development space. She also discusses management challenges for emerging biotechs and the leadership qualities that will make today’s CEOs fit for business in the 2020s.

As well as being CEO and co-founder of Theolytics, Casebourne, aged 26, is also a board member of the UK Bioindustry Association. Previously, she was a co-founder and director of the strategic consultancy group New Medicine Partners and she has held leadership roles within a number of organizations, including: curator of the World Economic Forum Global Shapers network; managing director of HealthTech Women London; and Hello Tomorrow’s London chair for health care and medical technologies.

Theolytics is built around core technology developed by Margaret Duffy, who is also

the company's chief scientific officer. The small biotech has 11 employees, primarily R&D focused, and has recently made additions to its board of directors. In June 2019, Ken Powell was appointed chair of the board – bringing significant virology and commercial expertise into the group, as a founder of Arrow Therapeutics and ReViral. Powell has led the development of multiple products including antiviral compounds against herpes viruses, HIV, hepatitis C and respiratory syncytial virus (RSV).

**In Vivo: Theolytics is sticking its head above the water, so to speak, and preparing for a Series A financing round. Why should people pay attention now?**

**Charlotte Casebourne:** It is an interesting situation when you are an early-stage company: how do you balance making sure the right people know that you exist, with not giving away your competitive advantage while you're still emerging? After a period of rapid development, we are now establishing the systems that we need to build sustainability through to the next phase. We have not publicly disclosed the target amount for the Series A round, but I can confirm that we are currently raising the resource that will enable us to clinically validate our core technology platform. We want to ensure that we are moving fast and using our capital efficiently in order to quickly prove the potential of what we are working on.

**What do you see as the biggest challenge in cancer drug development today?**

Differentiation. It is a busy space. More drugs have been approved in oncology than any other therapy area since the 2000s, and the number of active compounds in oncology R&D has doubled since 2008 representing around 40% of the global clinical pipeline.

We are experiencing an exciting new wave of therapies coming through, including potential cures such as Merck & Co. Inc.'s PD-1 inhibitor Keytruda (pembrolizumab). Working on incremental technologies that are going to have marginal improvements for patients is not going to stand-up anymore in what is an incredibly busy space. Differentiation –

significant differentiation – is important.

Another challenge – which is also representative of progress in the field, though perhaps a double-edged sword – is the increasingly sophisticated stratification of patients. Over a third of clinical trials are now using biomarkers to stratify patients; this is unprecedented. Chimeric antigen receptor T-cell (CAR-T) therapy, for example, is exquisitely personalized to a single patient. This represents a challenge when it comes to the health economics of some of these drugs.

When price points rise to the level that they become a serious barrier to patient accessibility, this is a critically important challenge. Within the immunotherapy space we are seeing eye-watering prices, which is just one of the reasons viral therapies for cancer represent an attractive approach. We are not quite talking the same price as a vaccine, but oncolytic viral therapies have the potential to be much closer to the cost of a vaccine than that of a CAR-T treatment. This is important when we are working towards ensuring that patients all over the world have access to effective drugs for cancer.

**Thinking about differentiation, what sets Theolytics apart in oncology?**

Oncolytic viruses are particularly interesting within the immuno-oncology space; they represent a unique therapeutic paradigm. First, oncolytic viruses can selectively infect even very heterogeneous tumor types. Unlike an antibody or a CAR-T therapy, these viruses are not dependent on a single surface marker to infect. Their ability to be effective even in heterogeneous tumors is an important differentiator. If one looks at the market today, there are either these exquisitely targeted options or something like chemotherapy, which just kills rapidly dividing cells in an undifferentiated manner; there aren't many options in the middle.

Second, oncolytic viruses are interesting because the dose is amplified *in situ*. These are one of the only types of therapy where you can amplify the dose that you want to expose the patient to in an exquisitely selective way, exactly where you want your dose to increase.

Third, the viruses can even activate the immune system in "cold" tumors. There has already been some nice early data

from oncolytic viruses in combination with checkpoint inhibitors like Keytruda and Bristol-Myers Squibb Co.'s Opdivo (nivolumab). Checkpoint inhibitors are not effective in patients who have cold tumors, where the immune cells are not present. So, viruses are able to pull immune cells into the tumors. Therefore, we are seeing some synergistic effects for oncolytic viruses in combination with treatments that are already available but are otherwise ineffective for many patients. We are in a strong position now to start thinking about combination approaches.

Theolytics works with adenovirus. We can arm that virus with almost any genes. This ability to potentially deliver additional therapies by arming our viruses means that there is a useful niche within the oncology space.

Furthermore, viral manufacture is significantly less expensive and the product is easier to distribute than most immunotherapy products. This opens up global markets to us that might otherwise be inaccessible.

**You mentioned biomarkers and there use in clinical trials today, but how else have you seen the R&D sector change in recent years?**

It's interesting to look at the dramatic changes in the industry over the last five years. My role on the BIA board has provided valuable visibility over both historical trends, and how the sector is evolving. For example, it is evident that over the last five years major pharma companies are increasingly outsourcing R&D activities to smaller, more nimble biotechs with successful results. An example here would be Gilead Sciences; most of their lead products are the result of external licensing deals, and have not come through from internal R&D pipelines.

When we look at how innovative some of these big pharmas are, one of the reasons Gilead stands out is because over 60% of its 2018 revenues came from products launched over the last five years. To put this into context, that is six times higher than the average of the top 30 companies in some comparisons and is an interesting surrogate for how "fresh" (or stagnant) some of the incumbent big pharma pipelines are.

There is a disparity between the

percentage revenue coming into these companies from new products versus old. When we look at those companies doing well in terms of the “freshness” of their pipelines, a lot of those products are coming from licensing deals and acquisitions. It goes some way towards demonstrating how the different stakeholders within the R&D sector can capitalize on what they’re good at. For some of the bigger players, that might not necessarily be doing innovative R&D in-house.

**What excites you in the oncology space when you are looking at development trends and innovation?**

There are multiple converging technological advances that are enabling us to develop better therapies – that are more selective and more potent – and to do that faster. At Theolytics, our core technology platform is powered by three enabling technologies. Each of those technologies has really emerged over the last three to five years.

The first of which is long-read sequencing technologies. The reason the long-read sequences are important for us, is because the viral genome is genomically diverse. We had to find a way to characterize the viruses that we are working with, both as drug candidates, and in the form of pooled virus libraries. We wouldn’t be able to do that if we didn’t have access to these advances in technology.

The second enabling advance is within genetic engineering technologies. These technologies allow us to exquisitely manipulate the genome in a way that we have never been able to do before. We can pull drug candidates out of our libraries using a “Darwinian” selection approach, as opposed to what the field has historically done, which is to use human brain power to rationally work through what the best virus sequence for a given indication might be. Our approach speeds up timelines from what historically might have been five to 10 years, to six to 12 months for us to pull out a good drug candidate.

The third technology that’s accelerating development for us is advances in bioinformatics. These have improved our ability to work in a sophisticated way with the sequencing data that we generate. We are building rapid feedback

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*“To develop and deliver great products to the market in a changing landscape you need to have a finger on the pulse of the sector.”*

*Charlotte Casebourne  
Theolytics CEO*

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loops into the drug development process so that we can start to apply a tech company mind-set within the life sciences. The data points that we are generating improve our ability to be responsive and iterate quickly.

**Was the goal always to be a “platform technology” company?**

We were never interested in being a single-asset company. With Theolytics, we are working towards revolutionizing the way in which oncolytic viruses are discovered and developed, and are building what we need within the company to ensure that we are best placed to lead that shift in the field. What our platform enables us to do is to identify highly efficacious, selective drug candidates within diverse virus libraries, and we can do that rapidly, across a broad range of indications.

**What are the big milestones coming up for Theolytics?**

We’re working toward regulatory enablement with IND submissions for two lead assets, with the aim of instigating clinical trials in 2021. These are the big milestones. We will be building out our team over the next 12 months to enable us to successfully achieve these goals.

**What was your first role in the life sciences industry and how did that lead you toward being a CEO today?**

I was exposed to patients first, and I think that has shaped a lot of my perspective of the life science industry. I lost my grandmother when I was a child, and that was my first exposure to the challenges within the health system. I went on to volunteer in Denmark Hill Hospital in South London while I was studying through my undergraduate degree, primarily working in geriatric and oncology wards. I realized that in many instances the clinicians did not have the tools that they needed to support patients, and decided that that was the problem that I wanted to work on.

As an industry it is critical that we do not forget the people that we are serving. Keeping patients front-of-mind has driven Theolytics to establish a network of exceptional key opinion leaders within the clinical setting to ensure that we are accessing the breadth of expertise and

perspective that we will need to deliver life-changing therapies.

### What skills are required to be a biotech CEO today?

Stamina, energy and commitment. It is a long game. We are setting audacious goals and intend to see them through. One thing that is critically important is the ability to learn quickly. It is a complex environment to be operating in; no one person knows everything. You have to learn enough to be able to ask the right questions and also have the humility to seek out individuals who know more than you do. The last thing I'd add would be perspective – the ability to zoom out. To develop and deliver great products to the market in a changing landscape you need to have a finger on the pulse of the sector. This is an additional way in which my involvement with the BIA has been invaluable: access to the information that enables us to zoom out and take stock of the international environment that we are operating in. This is an important

contribution that the organization makes to the UK Biotech sector.

### What is one of the most difficult parts of your job?

Finding brilliant people is one of the hardest but most important challenges as Theolytics grows, and we are increasingly seeing Oxford companies attract talented individuals from all over the world. I am fiercely proud of our team at Theolytics; there are few things less important than finding great people to work alongside. Finding the right people, building that high-performing team is challenging but critically important. It takes time.

### Do you have any concerns around accessing talent, considering external issues such as the unstable situation around Brexit?

We're not coming up against issues yet. However, there is a concern that the situation might change, especially with some of the more senior roles that we are looking to recruit for. Whatever change

does happen, for the right person we will always go above and beyond to make sure that we can find a way to enable them to join the team. The right person is the most important factor.

### What is the one myth or misconception about the biopharma industry that you would like to set straight?

The myth within the industry that I would like to set straight ... it is that drug prices can keep getting higher and it will not affect access because payers will cover the costs. Exorbitant drug prices do contribute to decisions by payers to restrict or ration treatments. It is not about undermining our ability as companies to be commercially successful, to generate revenue that will allow us to sustain growth and to continue to invest in developing great therapies. But the balance is important; the balance between greed, sustainability and fairness. ✪

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#### Comments:

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# Going Back To The Future To Treat Diabetes



Applied Therapeutics has a business model that defies the conventional wisdom about start-up success: reviving science abandoned by big pharma; financing from a narrow group of investors, dependent on the goodwill of a single academic institution; all in pursuit of a small molecule solution to one of the biggest, diversely complex and cost-defying challenges in chronic disease – the complications of diabetes.

## BY WILLIAM LOONEY

The company targets the unmet need for treatments that inhibit the pathogenic actions of a single protein enzyme – aldose reductase – in three specific conditions related to type 1 and 2 diabetes: diabetic cardiomyopathy, galactosemia and diabetic retinopathy.

The company evolved from basic research on aldose reductase conducted by a Columbia University lab led by Dr. Donald Landry, with critical IP support from Columbia's Tech Ventures group.

So what? Complications from diabetes is a public health challenge of epic – and global – proportions. Even if its trials meet their endpoints, Applied Therapeutics Inc. will require additional capital and support to prevail with its full-in, stand-out business model.

**A** big challenge facing biopharma today is to grow revenues, mainly through the timely introduction of market-pleasing new products. That is getting harder as an abundance of new science extends the range of possible targets and as precision medicine fragments diseases into subtypes based on complex variations in pathogenesis, right down to the individual level.

One lead generating strategy that holds promise is literally going back to the future – returning to treatment pathways abandoned because they had proven difficult to drug, this time using enhanced understanding of disease pathology to expand that druggable space with molecular targets that are highly selective, less toxic and more potent. The idea is to combine the legacy science with newer drug design technologies like automated crystallography, which can detail a molecule's structure faster and more accurately than was the case a decade ago. By unplugging the bottlenecks to proving safety and efficacy that caused the earlier work to fall short, drug developers can gain a lock on approval for small molecule therapies addressing some of the biggest areas of unmet medical need.

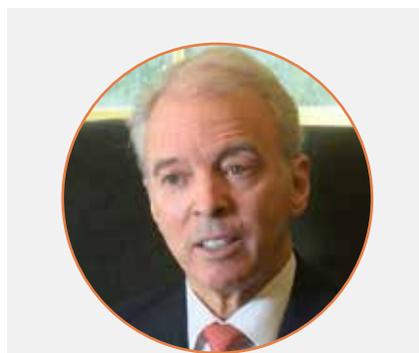
Finding treasure in discarded science is not without risks. But interest in the strategy is growing now that big pharma has embraced external innovation and academic researchers to look for ways to progress beyond the lab work that often reflects years of commitment to a single pathogenic target. One start-up has even named itself after the concept: Applied Therapeutics Inc., founded in 2016 to apply new technologies to prior validated targets. One such target is a common enzymatic protein, aldose reductase, whose activity influences the metabolism of blood sugars like glucose and galactose. A higher level of aldose reductase is associated with inflammatory toxicity and cell death in the vascular system, including the heart. It is most evident in the nerve,

cardiovascular and ophthalmologic complications that accompany diabetes, but aldose reductase has been shown in mice studies to also be a factor in sepsis, asthma and some cancers.

The basic work in identifying the link between aldose reductase and disease goes back decades. Big pharma, including **Pfizer Inc.** and other companies, sought in the early 1990s to commercialize drugs to reverse the effect of the aldose reductase enzyme in causing chronic debilitating conditions due to diabetes. Despite heavy investment, none of the companies' candidates – Pfizer's zopolrestat did make it to Phase III – progressed rapidly enough through preclinical and clinical development to get to market. In the end, only one aldose reductase inhibitor, Ono Pharmaceuticals' epalrestat, was approved, in 1992, only in Japan and for a single indication of diabetic peripheral neuropathy. Soon after, US and European drug makers abandoned the effort to commercialize the enzyme.

A decade later, at the Columbia University lab of Professor Anne-Marie Schmidt, progress revived around the underlying biology of aldose reductase. Schmidt, an MD biologist and leader in auto-immune/inflammation research, discovered a cell-surface receptor for advanced glycation end-products (RAGE) that, when activated, exacerbates heart disease-related vascular injury, particularly in diabetics. Schmidt advanced the basic science and refined a preclinical assessment of aldose reductase inhibitors in diabetes and in coronary artery reperfusion.

But work could not get into the clinic unless a new small molecule aldose reductase inhibitor could meet the patent threshold necessary to enable investment in the final development phase of research. The Columbia Tech Ventures (CTV) group, which handled tech transfers for the University, knew IP was a limiting factor that frequently threatened promising projects like this one. CTV was able to put forward a potential solution: Columbia Professor Donald W. Landry. Landry, a physician and PhD in organic chemistry with an enterprising nature reflected in the 46 patents he held on his own work, had in 1998 founded and directed a new Division of Experimental Therapeutics at Columbia's Department



– DR. DONALD LANDRY  
OF COLUMBIA MEDICAL  
SCHOOL

of Medicine. He also attracted support from the biopharma industry to establish an Organic Chemistry Collaborative Center (OCCC) in the department to synthesize small molecules to validate novel targets for drug discovery – in effect, weaponizing all those earlier forays in the lab. CTV also helped the cause with its practice of reviewing reports of all inventions coming out of the Medical School to identify protein targets that could be forwarded to the OCCC to test as viable drug candidates.

In an interview with *In Vivo*, Landry said “our reading in the case of aldose reductase inhibitors was that industry researchers had made enormous progress. The problem for them was time. The clock ran out on patent protection and it just became untenable to keep pressing forward.” Landry, who now heads Columbia's Department of Medicine, touted the university's strength in developmental science through the OCCC combined with a highly entrepreneurial tech transfer operation as a reproducible platform for commercializing ideas with IP. “The question I often get is why choose aldose reductase inhibition from all the projects that come up in a given year? The answer I give relates to the vast unmet medical need associated with the persistent burden of complications from diabetes. We had some spectacular preclinical data from the Schmidt team as well as all the legacy work in big pharma. That led us to take a shot at producing a new composition of matter patent portfolio for aldose

reductase inhibition. With a new IP position, the project could advance through human clinical trials and perhaps change the woeful standard of care for patients.”

An OCCC chemist, Andrew Wasmuth, took on the work of creating a molecule with a novel aromatic core. He devised the method to prepare it in pure quantities, reproducibly at scale. “The chemistry was extremely difficult, and it took us eight months to perfect something that worked at high yields. It was an extraordinary achievement by Wasmuth, and also confirmed the validity of the big investment that Columbia had made in this field, unusual for a medical school,” Landry said. The technology was more favorable too. The OCCC was also able to take advantage of recent advances in crystallography that enabled the team to quickly develop a set of detailed crystal structures of the aldose reductase enzyme – a process that in the 1990s would have taken years to complete.

### Seven Years To Success

The collaboration between Columbia biologists and chemists finally developed a compound to block the aldose reductase enzyme with improved efficacy and safety compared to earlier drug candidates. This small molecule, patented by the CTV group, had higher selectivity in targeting the enzyme and was approximately 100 times more potent than earlier inhibitors. But while there was enough data from *in vitro* studies to conclude that the compound potently inhibits the enzyme, efficacy in humans was only a hypothesis until Applied Therapeutics began testing to confirm these effects in human clinical trials.

Indeed, Landry's progress in making aldose reductase druggable might have simply sat in the “nice, but so what” file had it not been for a young Columbia PhD graduate in neurobiology who decided to forgo teaching and research for a career evaluating clinical targets for big pharma companies seeking to fatten their pipeline portfolios. “I chose consulting over research because I wanted my interest in science to mean something beyond publishing a peer-reviewed study,” said Shoshana Shendelman, now the 41 year-old CEO of Applied Therapeutics, the start-up focused on commercializing

Landry's research, in an interview with *In Vivo*. "As a Columbia graduate, I knew about CTV's licensing unit and usually got a first look at things it was putting out there from the research faculty. Landry's work for the aldose reductase inhibitor small molecule intrigued me from the start because the implications of this enzyme for disease are widespread, with the potential to impact so many people who don't have any drugs for their condition."

At first, Shendelman thought a license might be an attractive fit for one of her big pharma clients. But as her due diligence progressed, she began to doubt whether any big pharma firm had the will to turn Landry's small molecule into a drug that could work in patients. "When projects fail in big pharma, as it did in the 1990s for a large, high-potential therapy class like diabetes, there is a stigma that can last for years." And while the drug majors had the resources to mount large development programs around multiple indications, would process issues, competing pipeline priorities and frequent management changes intervene to slow things down?

Shendelman concluded that a science-minded biotech culture might be better in going after niche indications with the highest unmet medical need instead of taking a commercial perspective to secure the largest market possible, which would take much longer. "For the worst complications of diabetes, like diabetic cardiomyopathy, there are no drugs available – quite simply, it's fatal. And the sicker the patients, the more likely a treatment could benefit from the FDA's abbreviated development incentives, lowering the scope and cost of trials to speed access to the market. Both factors are extremely motivating to a biotech," she noted.

What Shendelman ended up doing was to put herself forward. "I met with the CTV team. I went out of academia to talk to industry, patients and practitioners. And I sat down with Dr. Landry, telling him I wanted to bring an aldose reductase inhibitor to patients at an accelerated pace – and the best way to accomplish it was as a start-up biotech with a single-minded commitment to progressing his asset to the clinic. I bluntly asked him to grant me the license to develop his work on the enzyme



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*“When projects fail in big pharma, as it did in the 1990s for a large, high-potential therapy class like diabetes, there is a stigma that can last for years.”*

– SHOSHANA  
SHENDELMAN  
CEO OF APPLIED  
THERAPEUTICS

”

into an approved drug in return for which I would form a company, raise funds and eventually take it public, with access to sick patients as our immediate priority.”

Shendelman emphasized her roots at Columbia already made her familiar with the science while the company would be small enough to give that science maximum attention – no chance of taking the big pharma route of parking the asset in a committee slot for years. She also committed to getting the new enterprise off the ground with several hundred thousand dollars of her own money.

Landry was convinced. That was enough to persuade CTV to grant the license to what became Applied Therapeutics. It met the cash-strapped company halfway by accepting low royalties on the license in return for a five per cent ownership stake and a position as a board observer.

### Different Strokes

Applied Therapeutics launched in January 2016 with Shendelman as chair and CEO and Landry as chair of the new company's scientific advisory board, which also includes two renowned experts in cardiovascular disease research: Gregg Stone, also of the Columbia Medical School, and Roxana Mehran of the Mount Sinai Medical School. Stone had worked closely with Landry in identifying the disease-inducing properties of the aldose reductase enzyme; both he and Mehran have extensive backgrounds in the design and oversight of cardiovascular clinical trials.

From the start, Shendelman held to a business commercialization plan centered on three simple fundamentals:

“I knew what I wanted to do. As an academic and later in consulting, I did development work in rheumatoid arthritis and multiple sclerosis, where the assignment was to commercialize the 15<sup>th</sup> drug for this and the 20<sup>th</sup> drug for that. It's an eye-opening experience when you face a situation where there are zero treatments for a life-threatening illness,” Shendelman said. “Seeing it from the patient's side completely changed my mindset. To see these people who have been left behind and to be able to offer them something is work worth doing – it's a public health issue and also in the public interest.”

Shendelman's plan may have been

simple, but it required a lot of explaining to the VC community, many of whom doubted the feasibility of a biotech start-up working in high-rent research precincts like metabolic and cardiovascular disease. The top of mind question was about the resources available to the company to compete – wasn't rare disease a better play for a start-up? Aren't big, multiple indications the provenance of big pharma?

Still, the new company was able to raise \$35m in series A and B financing in 2017-2018, due largely to its association with CTV, as well as timely support from Joel Marcus, the rainmaker CEO and founder of Alexandria Real Estate Equities and Alexandria Venture Investments. Analysts interviewed by *In Vivo* confirmed that Applied Therapeutics eschewed the big pitch campaign and instead focused on a small group of investors, which it was able to do through the reflected glow of its academic connections to the top scientists at Columbia University and CTV.

Shendelman also runs a tight ship. "All of our initial series A financing went to drug development. I had no employees the first year and my personal investment was allocated to the legal and administrative requirements to set-up the new company. All the VC financing was devoted to things like preclinical studies, talent recruitment, and manufacturing and operations assessment. And we assigned to ourselves a very aggressive timeline in starting the clinical phase of development of the aldose reductase inhibitor portfolio within the first year of our obtaining the series A – a goal that we've met."

Another milestone on the financing side was the IPO for four million shares issued on Nasdaq on May 13, the net proceeds from which totaled \$34m. Together with approximately \$15m in cash on hand, this gives Applied Therapeutics the runway needed to pursue its clinical development objectives for the next two years.

Shendelman said that being a public company had on balance been advantageous. Concerns that it would lead to a distracting blizzard of regulatory and filing requirements proved unfounded. "Since the IPO I think what has changed the most is I can get back to the business. We no longer have the issue when

we were private of hitting one milestone and then having to go right back out and solicit more funds. With the IPO, we now have a small, tight groups of investors who are going long on the stock so there is less likelihood of volatility in the share price." In addition to making the key appointments of a chief medical officer and a full-time CFO earlier this year, Shendelman has brought in a former head of capital markets at the law firm Skadden Arps, Stacy Kantor, to serve on the company board and oversee the compliance duties required of a public company.

### Three Shots On Target

With its credentials in place, the company is moving forward on its pipeline consisting of three drugs to address underserved conditions linked to diabetes and induced by the aldose reductase enzyme. The choices resulted from the extensive screening of compound properties that Landry and his team at Columbia conducted, based on this premise: now that we have identified aldose reductase as a major contributor to the complications of diabetes, what can be done to ensure that an AR blocking inhibitor can perform effectively and deliver its intended prophylactic effect?

Shendelman said, "We found through this screening how to deliver an oral drug and focus its payload directly on the back of the eye, or to be able to penetrate CNS defenses like the blood-brain barrier. Having a safe and effective aldose reductase inhibitor that is also CNS penetrant was a ground-breaking opportunity and guided us toward two of our three drug candidates – it was a precisely targeted approach rather than just casting a line out and hoping for the best." She contends the careful approach explains that, while Applied Therapeutics' pipeline may be short, it is heavy with assets that have progressed quickly to the review stage. "All our trials are pivotal which is unusual for a company only three years old."

The lead compound, AT-001, is an oral small molecule drug with an initial indication for adults with diabetic cardiomyopathy, a progressive and fatal fibrosis of the heart. A Phase I/II randomized, placebo-controlled trial of the drug was launched in January 2018 involving 120 patients, all with type 2 diabetes, who

were subjected to a dose escalation protocol designed to assess tolerability and safety of the drug along with its specific pharmacokinetic actions and properties. The study also evaluated a biomarker of cardiac stress, NT-pro-BNP, for its use in predicting the pathology of heart failure.

Results of the year-long trial, presented at European Society of Cardiology in May and at the American Diabetes Association in June, showed AT-001 met its endpoints. The drug was well tolerated at all dose levels, and was both potent and selective in inhibiting the effect of aldose reductase in raising the level of sorbitol, the blood sugar known to induce cell death and fibrosis in the heart muscle.

The outcome puts the company on course for the pivotal Phase III trial needed to secure an NDA for AT-001 and eventual approval by the FDA. It will draw on a considerably larger number of enrolled subjects, from sites in the US, Europe and Canada. Shendelman noted, "What puts us in a good position to go forward quickly with this is that all our enrolled patients can remain on their standard-of-care meds during the trial, so if their primary physician doesn't like their HBA1C (blood sugar) score, he or she can switch them to something else without affecting our protocol."

She also noted that the clinical program would include patients with both types of diabetes. "People often forget that diabetic cardiomyopathy presents in type 1 patients, many of whom are quite young – they could be age 30 with 10 or even 20 years of complications from their condition behind them. Heart failure at such an age is an even bigger tragedy and raises significant questions about the impact an effective treatment could have on premature deaths from cardiomyopathy, from an economic productivity or societal well-being standpoint."

The second drug in the Applied Therapeutics pipeline, AT-007, targets galactosemia, a rare genetic disorder that affects the body's ability to metabolize galactose, a sugar produced at low amounts in the cell but is also found in milk and other dairy products. The condition is fatal in infants if it is not promptly diagnosed after birth and treated with a highly restricted diet. And even with dietary controls there can be serious long-term complications ranging



Among the many complications associated with diabetes, chronic heart failure (CHF) stands out as perhaps the least understood. This is despite growing awareness that CHF is a key but often hidden contributor to mortality from diabetes because it can progress for years without symptoms in diabetic patients until the late phase, when fibrosis of the heart ventricles are so pronounced that there is no recourse – many patients with diabetic cardiomyopathy die within a year and a half of diagnosis.

Only recently have research studies begun to reveal the pathophysiology of heart failure in diabetic patients. The standard classification of CHF into two aspects – heart failure with preserved ejection (HFpEF) and heart failure with reduced ejection (HFrEF) – is seen by many clinicians as inadequate in building a reliable taxonomy of the disease. Datamonitor Healthcare’s latest forecast for the CHF drug development space, published in March 2019, notes that for the most common presentation of CHF, HFpEF, “patients don’t have the benefit of a specific treatment plan, while many existing pharmacologic treatments have been shown to be ineffective.”

That said, overall the potential drugs market in CHF is buoyant, with Datamonitor forecasting a more than 12% compound annual growth rate to 2026, led in part by label expansions for the sodium-glucose cotransporter (SGLT-2) inhibitor class already indicated for type 2 diabetes, to cover type 2 patients at risk of heart failure who also suffer from diabetic nephropathy. The problem for diabetes patients is the most common way they experience CHF, through cardiomyopathy, has no approved treatment for it.

Feeding the interest in treatments specifically for diabetic cardiopathy is a stark statistic from the federal Centers for Disease Control and Prevention: one in every nine deaths in the US include heart failure as a contributing cause, with diabetes as the most prominent originating culprit. The cost of this proliferating cycle of chronicity is estimated at more than \$30bn annually from lost productivity and repeated hospitalizations – almost a third of the US population with heart failure ends up in hospital at least once every year.

Diabetic cardiomyopathy leads to heart failure through its degenerative impact on the heart muscle; and is ultimately fatal to the more than 70 million diabetes patients worldwide who contract it. That burden looks set to continue. A

longitudinal study, *Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes*, published in April 2017 in the *New England Journal of Medicine*, used 14 years of data from Sweden’s National Diabetes Register to examine cardiovascular outcomes and mortality risks for patients with both type 1 and type 2 diabetes covering six areas: deaths from any cause, acute myocardial infarction, coronary heart disease, all cardiovascular disease, stroke and heart failure. Progress was noted in the significant reductions in rates of mortality and complications in all cardiovascular indications, with the notable exception of heart failure, which evidenced higher increases in hospitalization in patients with type 1 diabetes. The study attributes the discrepancy to heart failure being a “neglected complication of diabetes,” and suggests “other processes, less well appreciated and therefore less well treated, that contribute to heart failure risk are not affected by contemporary clinical care for patients with type 1 diabetes.”

In other words, there is a significant unmet medical need centered on diabetics who need treatment to repair the damage that uncontrolled high blood glucose levels causes to calcifying blood vessels and fibrosis of the heart muscle. Encouraging drug developers to address this need was the implicit message in a draft industry guidance, *Treatment for Heart Failure: Endpoints for Drug Development*, issued by the FDA on June 18. The document seeks to clarify what FDA says is a belief by some drug sponsors that “favorable effects on mortality and morbidity – specifically, hospitalization for heart failure – are required to approve drugs to treat heart failure.”

The FDA draft guidance says that’s inaccurate. While important, favorable effects on survival and hospitalization rates are *not* required for FDA approval. “The type of evidence of efficacy needed to support approval of drugs for heart failure does not differ from the evidence needed to support the approval of drugs intended to treat other conditions: substantial evidence demonstrating that the drug improves how a patient feels, functions (i.e. symptomatic or functional improvement) or survives.” It adds that the benchmark for a functional or symptomatic improvement requiring additional mortality data is comparison to mortality and other safety findings for existing, pharmacologically similar drugs like ACE inhibitors or beta blockers.

Applied Therapeutics Inc.’s CEO Shoshana Shendelman said the message to novel drug developers interested in tackling diabetes complications as a pathway to heart failure was clear: “talk to us.” The FDA is clearly interested in consulting on how the regulatory process can facilitate more innovation to fight this deadly convergence in today’s rapidly aging society. ❖

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from neurological and motor impairment to eye cataracts and speech limitations.

In May, the drug obtained orphan drug designation from the FDA, allowing the company to qualify for seven years of market exclusivity after approval as well as fee application offsets and tax credits to help reduce development costs of the drug. However, Shendelman said galactosemia's classification as a rare disease is not what motivated its placement in the pipeline. "The level of unmet need in galactosemia is what was attractive to us, especially the long-term consequences it poses for children as they become adults. The co-morbidities make fighting this disease a public health priority that can be addressed quickly through commercialization rather than charity."

Applied Therapeutics has also signed a partnership agreement with Emory University in Atlanta to conduct preclinical research on how aldose reductase inhibition can counter the complications associated with galactosemia. This work figures in a Phase I/II trial the company launched in June, consisting of two cohorts: a profiling test for aldose reductase inhibition among healthy volunteers, already underway, and a cohort of adult subjects with galactosemia that will launch in September. There are plans to include a pediatric component as well. All this is being posted as a pivotal trial, designed to support FDA approval, and the hope is to have results ready to file with an NDA in late-2020.

The third compound, AT-003, is an oral adult treatment for diabetic retinopathy, a condition that is the leading cause of blindness in the adult population, affecting more than three-quarters of long-term diabetes patients. Landry's original research found that aldose reductase is associated with cell death and vascular and neural degeneration of the retina, leading to loss of normal blood flow and the release of membrane-damaging toxins as occurs in ischemia. Existing treatments for diabetic retinopathy require injections into the eye, performed outside the home in a clinical setting. As an oral pill, AT-003 is thus positioned to be a potential advancement over current standard of care.

Over the past two years, the company has conducted a number of preclinical animal studies on AT-003 – no work has yet been done with human subjects. The

plan is to review this work and initiate a Phase I/II trial for AT-003 next year.

### Looking Forward – Fresh Play In Cancer

Now that Applied Therapeutics has achieved its IPO objective and set the clock on a pathway to commercialization on three targets aimed at the aldose reductase enzyme, what are the milestones to be secured – what will the company look like well into the next decade? Shendelman said her focus would be on successful drug launches, specifically for the indications galactosemia and diabetic cardiomyopathy, and especially in the latter case, where the financial stakes are highest. Another is building out the organization's inventory of talent: at present, Applied Therapeutics has only 10 full-time employees. That number is destined to grow over the next year, although the desire is to stay lean and avoid a situation where the company's scientific advisory board might have to negotiate for face time with management.

Access to fill the unmet medical need in diabetes is central to Applied Therapeutics business mission, so a pricing and reimbursement strategy will also be a focus going forward. It is a sensitive issue for everyone in biopharma, but Shendelman looks at it as a manageable one – handled correctly access can be positioned as a reputational asset for the company. "First, we don't face the situation where there are competing products already available and you have to fight to win market share. Our science is original, patented and competitors against our unique platform really don't exist now. We launch into a population that is getting sicker and has few options; everyone is willing to engage. Most important, our therapies are not biologics but small molecules that can be manufactured and distributed at lower cost. We follow an abbreviated development model, repurposing and refining the basic research that has already been done. That also gives us a savings advantage over conventional R&D. Taken together, we see a lot of flexibility and good will waiting for us on market access. Applied Therapeutics is going to price responsibly because it's right – and because we can."

Despite the inventory of positives, it is still speculation. The company today has

no products. Yet investment analysts have tended to under-estimate the company's prospects, said Shendelman. She acknowledged some pushback from those in biopharma who said the requirements for getting anything approved in metabolic disease were dauntingly expensive – there is never enough money. Fast followers are legion and expensive product rollouts can be inconclusive in terms of market acceptance. An established class of type 2 diabetes treatments – sodium-glucose co-transporter inhibitors (SGLT-2) – is being combed over to see if these might be indicated for the same disease complications Applied Therapeutics is pursuing. Informa Trialtrove's review of *2018 Completed Clinical Trials* finds the type 2 diabetes therapy area had the single biggest number of completed trials by industry sponsors last year – suggesting that competition may be on the way.

"When we talk to people outside our circle, it's often hard to get them to abandon the mindsets they're most familiar with. To paraphrase, 'We don't want to depend on large VC funding, a business dependent on unlocking secrets of a single complex enzyme is too risky, and biotech isn't suited to prosper in the wide-open cardiovascular field.' That's why right now the NASDAQ market is pricing us as a rare disease company with one asset. That's not who we are. I say we are a play that's deeply undervalued." Les Funtleyder, portfolio manager for esquared Capital Inc., and an investor in the company, agrees. "New technology is allowing us to look at old intractable problems in new ways. That's what excites me about this company."

Nevertheless, Shendelman is poised to do some de-risking of the company's all-in business model. Recently, the board agreed to license in a second technology, in the oncology space, specifically the phosphoinositide 3-kinase inhibitor class often administered in hematologic cancers when patients fail to respond to mainline therapies. "It's a different disease, but we intend to apply the same highly targeted enzymatic approach that we now have against aldose reductase in complications of diabetes." ❖

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#### Comments:

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# *In Vivo's* Quick Guide To Gene Therapy



Once the stuff of (largely implausible) science fiction, gene therapy is now a clinical reality and one that is taking an increasing share of the pharma R&D limelight. *In Vivo* takes a look at how these therapies work, how the field has emerged and where it is likely to go next.

## BY ALEX SHIMMINGS

Despite development challenges, the therapeutic promise of gene therapy has proved a lure for many firms. There are around 425 unique companies – acting as originators or licensees – with development-stage candidates.

In the gene therapy pipeline, one third of candidates are in development for rare diseases, about another third are targeting oncology indications, with the rest being explored in other therapy areas.

The real challenge for these products is to prove themselves on the market: can they move from curiosities to cash cows?

**W**hen it comes to taking medical science to the next level, gene therapy is one of the most exciting technologies out there. In attempting the leap from treatment to cure it holds the captivating promise of turning the once-miraculous – making the blind see, the lame walk, the deaf hear – into a clinical reality.

After a fitful start, these “miracle” cures are now reaching the market in sufficient numbers to drive huge investment and a wave of deal-making in the field. Still, gene therapy has much more to prove as a drug class before it can be secure of its place in the array of treatments available to doctors. As well as needing to confirm the durability of these products’ effects, there are issues over manufacturing, pricing and their commercial viability to contend with.

With critical mass achieved in both the development pipeline and public awareness, gene therapy looks like it is here to stay, but the field is complex and wide ranging. Here, *In Vivo* surveys the landscape.

### Where Did It All Begin?

Gene therapy was first mooted as genuine treatment prospect for human genetic diseases back in 1972 in a paper published in *Science* by Theodore Friedmann and Richard Roblin. Having made a survey of early research on the genetic modification in mammalian cells, they made their prescient conclusion: “In our view, gene therapy may ameliorate some human genetic diseases in the future. For this reason, we believe that research directed at the development of techniques for gene therapy should continue.”

While this did not prompt an immediate rush to the bench, the concept did gain traction and by 1995 there were around 100 gene therapy candidates in development.

Their numbers then increased steadily until 2003, when they hit 275. At this point the gene therapy category was the third largest in the overall R&D pipeline.

This was to prove an early peak. The death in 1999 of 18-year-old patient Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania Medical Center was the first major check to the field, and a few years later the development of leukemia in four children in a French study dealt another heavy blow. Developers took fright, and the number of gene therapy candidates in the pipeline dropped, not to return to 2003's levels for more than a decade.

But this mini Dark Age fell mainly on the west: companies in Asia plowed on to quick success. In 2004, China approved the world's first gene therapy product – Gendicine, from the domestic firm Schenzen SiBiono GeneTech, for head and neck cancer – and a year later Shanghai Sunway Biotech launched Oncorine for head and neck and nasopharyngeal cancer, again in China. These were followed in 2006 by Epeius Biotechnologies' Rexin-G for solid tumors in the Philippines, and in 2011 the Russian Federation approved its first gene therapy.

These winds of success slowly cleared the cloud over the west and development there returned. The first regulatory triumph, uniQure NV's Glybera (alipogene tiparvec) in the EU, may have failed on the market, but it was followed in 2015 by approvals for Amgen Inc.'s Imlygic for melanoma in the US and EU. Two more products reached the market in 2016 and four in 2017 – all in western markets – as gene therapy finally went mainstream. Now a total of 13 gene therapy products have received approval somewhere worldwide.

These regulatory victories helped swell the number of gene therapy candidates in the pipeline to the point where there are now around 1,000. Gene therapy has remounted the podium as the third largest category in the overall pipeline, according to the drug database Pharmaprojects, lagging only two cancer groupings.

This renaissance was also catalyzed by the development of a solid regulatory framework in both the EU and the US around which companies could build their product research. Although the two regulatory agencies have slightly differ-

ing definitions of what they consider to be a gene therapy, there is much overlap (see Exhibit 1).

The European Medicines Agency (EMA) was off the mark much quicker, creating the advanced therapy medicinal products (ATMP) regulatory pathway back in 2007. This included gene therapies along with somatic cell therapies, tissue-engineered medicines, and “combined ATMPs” that have one or more devices integrated within the medicine.

In the US, gene therapies come under the Food and Drug Administration's regenerative medicine advanced therapy (or RMAT) designation, which came into existence in 2016 with the 21st Century Cures Act.

### How Do They Work?

Put simply, gene therapy seeks to treat or cure a disease by making changes to a patient's genome. This can be by introducing new nucleic acid code to the patient, by removing a faulty part of their code or by editing their genes to correct a defective sequence. These changes alter how a single protein or group of proteins is produced by the cell – they may reduce the levels of a disease-causing protein, increase production of a useful protein, or allow for the production of a missing protein or a modified protein.

Gene therapies, therefore, lend themselves best to certain types of disease: congenital genetic conditions and those that arise from a later gene mutation, such as cancer. Oncology indications account for just over half of the gene therapies already on the market, and they predominate those launched in western markets.

Of the pipeline, one third consists of candidates in development for rare diseases, about another third represents oncology indications, with the rest tilted at other therapy areas. Nearly half of the gene therapies in development for rare diseases target rare cancers. Popular non-cancer choices for development include monogenic diseases such as hemophilia, sickle cell disease, Duchenne muscular dystrophy and spinal muscular atrophy (SMA).

One point to note is that all gene therapies approved for human use so far are directed at somatic cells (specific types of already differentiated cells, such as lung, muscle or blood cells) rather than

in germline cells (the cells that when fully developed form into sperm or ova and are passed down the generations). Germline gene therapy is controversial, and the gene therapies developed for inherited genetic diseases act on patients' somatic not germline cells.

### In Or Out?

Gene therapies can be broadly divided by where the genetic modification is performed. An *in vivo* approach sees the modifications made in particular cells while inside the body, whereas *ex vivo* methods make their genetic modifications to cells, such as bone marrow or blood cells, that have been removed from the patient for that purpose; they are then reintroduced to the patient following gene transfer and cell expansion in the lab (see Exhibit 2).

Such *ex vivo* products are also known as “cell-and-gene” therapies and some of the front runners – most notably the CAR-T (chimeric antigen receptor T-cell) therapies Kymriah and Yescarta – fall into this class. These build on the older cell therapies that have been around in a primitive way since the advent of blood transfusions and bone marrow transplants.

Making a genetic change to cells within the body, with an *in vivo* approach, is a much trickier prospect, removing as it does the safety net of being able to check the correct alterations have indeed been made before the cells are returned to the patient. While it was not the first to reach the market, Spark Therapeutics' Luxturna, which was launched last year as a one-time treatment for an inherited retinal disease caused by mutations in both copies of the *RPE65* gene, was probably the most notable *in vivo* gene therapy on the market before Novartis AG's Zolgensma arrived.

The choice between *ex vivo* and *in vivo* approaches depends largely on the site of the disease and the accessibility of the target cells. The current pipeline is a near even split between the two approaches, with gene therapies having a slight edge over cell-and-gene therapies. *In vivo* delivery is weighted towards ocular disorders including retinitis pigmentosa and wet age-related macular degeneration, and in cancer towards solid tumor types, particularly liver and breast. The *ex vivo*

Exhibit 1  
Differing Regulatory Definitions

**EMA Definition**

- Contains or consists of recombinant nucleic acid, inserted into the body, to regulate, repair, replace, add, or delete a genetic sequence
- Has a therapeutic, prophylactic, or diagnostic effect that is related to the administered recombinant nucleic acid sequence, or to the resulting gene expression
- A somatic cell therapy or tissue engineered product that is also defined as a gene therapy
- Regulatory pathway eligibility: ATMP

**FDA Definition**

- Genetic material administered to modify or manipulate gene expression, or to alter the biological properties of living cells for therapeutic use
- Modification may include:
  - Replacing a disease-causing gene with a healthy copy of the gene
  - Inactivating a disease-causing gene that is not functioning properly
  - Introducing a new or modified gene into the body to help treat a disease
- Human gene editing technologies that disrupt harmful genes or repair mutated genes
- Patient-derived, *ex vivo* cellular gene therapies
- Regulatory pathway eligibility: AA, BTM, FT, PR, RMAT

LEGEND: ATMP = advanced therapy medicinal products; AA = accelerated approval; BTM = breakthrough therapy designation; FT = fast track; PR = priority review; RMAT = regenerative medicine advanced therapy

therapies tend to concentrate on blood disorders, particularly sickle cell anemia and thalassemia, and in oncology, on hematological cancers such as myeloma and acute lymphocytic leukemia.

The cell-and-gene therapies can be further divided into autologous (made from the patient’s own cells) and allogeneic (made from another person’s cells), with autologous dominating those products for which the type is known. Kymriah and Yescarta are both autologous, and some companies are looking to the next step, to produce an allogeneic CAR-T cell therapy product (also dubbed “allocart”). Allogeneic therapies promise an off-the-shelf product that would remove the practical and temporal pressures of creating a bespoke treatment; the downside is that they are more likely to provoke unwanted immune reactions.

CAR therapies account for the lion’s share of *ex vivo* gene therapy development in oncology: about 70% of the *ex vivo* segment is focused on this approach, which also includes other cells types engineered with CAR, such as natural killer cells.

**The Importance Of Vectors**

DNA is a delicate molecule so gene therapies need a delivery vehicle to get the new genetic information into its target cells for both *in vivo* and *ex vivo*

approaches. For most of the products in development, a virus is the delivery vector of choice, but there are some non-viral vectors being investigated. In this space, plasmids (small rings of double-stranded DNA that are distinct from a cell’s chromosomal DNA and can replicate independently) are the most popular pick but other methods include messenger RNA, liposomes and bacteria.

Viruses, however, dominate. They are ideally suited as they are evolutionarily designed for, and therefore very efficient at, getting their genetic material into host cells where they then co-opt the cells’ machinery to reproduce.

Different viruses do this in different ways. Some, such as adenoviruses, merely introduce their genes into the into the host cell cytoplasm where they produce gene expression that is transient (known as “non-integrating”). Others, namely retroviruses like lentiviruses, deliver their genetic code right into the cell nucleus where it is physically inserted into the host cell’s genome (known as “integrating”), resulting in a permanent change that lasts as long as the cell.

The choice of vector rests very much on what it is the developers are trying to do. Does the disease require long-term gene expression? Or will transient expression do the job? What vector will

work best for the particular target cell type? Many different viruses – including herpes simplex, influenza, vaccinia and measles – have been used to create gene therapy vectors, but four virus types loom large in the pipeline: lentiviruses, other retroviruses, adenoviruses and adeno-associated viruses.

Researchers transform these viruses into gene therapy vectors by replacing their disease-causing genetic code with the desired code to produce a therapeutic effect for the condition being treated, without affecting the virus’s ability to infect the cell. As a concept, this sounds straightforward, but in practice it is a lot more complicated – indeed, it was the vectors that caused the safety issues seen with the early gene therapy candidates.

**What Can Go Wrong?**

A host of pitfalls await the developer. For a start, the gene therapy might not work if the delivery to the desired cell type is inefficient. Some viruses are limited in the types of cells they can infect (something known as tissue tropism), and some may escape and infect distant sites with resulting difficulties.

With integrating viruses there is the risk of the vector injecting the new genetic material into a part of the DNA that causes harmful mutations that

cause like cancer, so-called “insertional mutagenesis.” This is what happened in the French study in 2003 in four patients with X-linked severe combined immunodeficiency (SCID) who received CD34+ hematopoietic stem cells transduced *ex vivo* with a retroviral vector: the therapeutic gene integrated into the *LMO2* proto-oncogene region and triggered the leukemia.

Other concerns surround the theoretical danger that the foreign DNA could enter the patient’s gametes (ova and sperm) and produce changes that would be passed on to their children.

Then there is the possibility that transferred genes could be over-expressed, producing so much of the protein that it becomes harmful, or the viral vector may get transmitted from the patient to other individuals or into the environment.

The vector may also cause an immune response – even a replication-deficient virus can retain enough of its original viral essence to stimulate the host’s defense mechanisms. This can lead to neutralizing antibodies and cellular responses that limit or even scupper outright any attempt to produce the therapeutic gene product.

Adding another layer of complication, some patients may already have antibodies against those vector viruses that commonly infect humans – these “inhibitors” leave recipients unable to benefit from gene therapy. Moreover, repeated administration of a vector in patients receiving a transient gene therapy may cause an inflammatory response, or patients may mount an immune response to the proteins expressed by the transgene itself.

And those are just the hazards posed at the patient level.

There are also major challenges that attend the large-scale production of viral vectors for clinical and commercial use. Viral vector manufacturing is probably the main rate-limiting step in cell-and-gene therapy.

Viral vector particle manufacture is cumbersome, time-consuming and expensive, and to date has been more of a custom process. Regulators are taking a keen interest in the area, with about 80% of the standard review time for gene therapies in the US being spent on manufacturing and quality concerns,

## DIFFERENT VIRAL VECTORS

### Retrovirus

Retroviruses have single-stranded RNA genomes, which are copied by the cell reverse transcriptase to create double-stranded DNA copies that then are integrated into the host cell genome, but only if the cells are dividing. Integrating retroviral vectors mediate long-term expression of transgenes in dividing and expanding cell populations, but in some circumstances have led to insertional mutagenesis.

*Used in: Invossa (now withdrawn), Rexin-G, Strimvelis, Yescarta and Zalmonis*

### Lentivirus

Lentiviruses are a subset of retroviruses, with an important difference being that they can be used for *ex vivo* and *in vivo* gene transfer into both dividing cells and non-dividing cells. They also have the advantage of broad cell tropism, in that they are also capable of stable transduction (ie, introduction of the foreign DNA into the cell) into many mammalian cell types.

*Used in: Kymriah and Zynteglo*

### Adenovirus

Another popular choice, adenoviruses readily infect human and other mammalian cells, and they can transduce both dividing and non-dividing cells. On the negative side, they are associated with a lack of sustained transgene expression and some doubts have been raised about their efficacy.

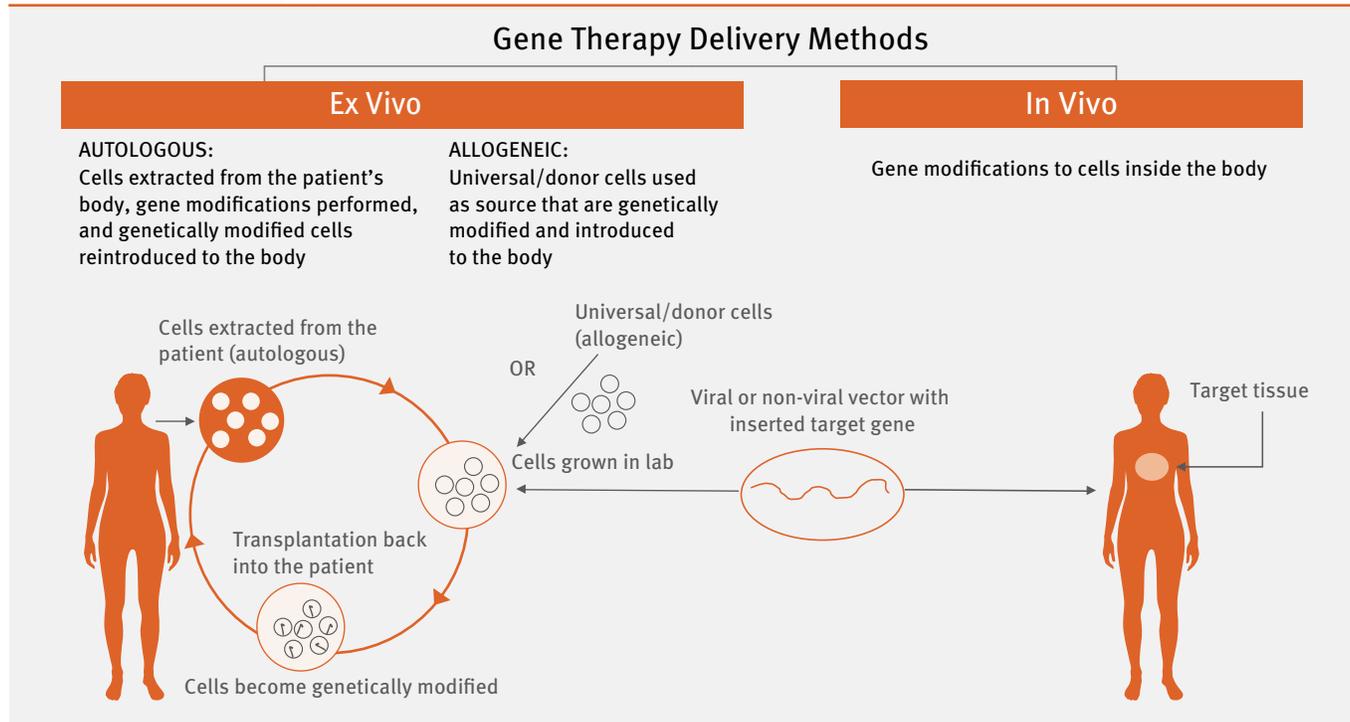
*Used in: Gendicine and Oncorine*

### Adeno-associated virus

Adeno-associated viruses are the most popular vector choice, for a number of reasons. These small, single-stranded DNA viruses can insert their genetic material at a specific site on human chromosome 19, enabling long-term transgene expression. AAVs can transduce both dividing and non-dividing cells. In non-replicating cells, AAV vectors are thought to persist as non-integrated, non-replicating episomes, so that long-term transgene expression can be achieved without integration. AAV vectors have low immunogenicity in humans, and are therefore seen as the most promising gene delivery candidate for conditions that need long-term treatment. AAVs also appear safer as recombinant AAV particles may be produced without any viral genes.

*Used in: Luxturna*

**Exhibit 2  
Gene Therapy Delivery Approaches: Ex Vivo Versus In Vivo**



and sponsors are encouraged to have meetings early on to discuss the issues.

Into the gap are stepping contract manufacturing organizations or contract development and manufacturing organizations specializing in cell and gene therapies, and more are expected to emerge, but even then demand is likely to exceed supply. A few companies, like bluebird bio, have developed their own capabilities but in future it looks likely that companies will hedge their bets and opt for both solutions.

**Who's Who In Gene Therapy**

Despite the difficulties, the therapeutic promise of gene therapy has proved a lure for many firms. There are around 425 unique companies – acting as originators or licensees – with development-stage candidates. These include very small players working on only one or two therapies to more active companies with larger pipelines upwards of 20 programs.

Big names such as Novartis, Roche, Amgen and Celgene figure, thanks in part to the deal making that has begun to characterize the field. Sanofi, Biogen Inc., GlaxoSmithKline PLC, Pfizer Inc., Merck & Co. Inc. and Takeda Pharmaceuticals International also each have at least five gene therapy candidates in their pipelines.

Novartis was a CAR-T pioneer, scoring the first marketing approval with Kymriah, but it has since expanded its capabilities towards *in vivo* approaches through its ex-US deal for Spark's Luxturna and its acquisition of AveXis and, with it, the SMA therapy Zolgensma.

Kite was second to the CAR-T market with Yescarta, and is now a subsidiary of Gilead Sciences Inc. following one of the largest biotech acquisitions of 2017. It is testing a number of methods in its pipeline, including gene editing (with Sangamo Therapeutics), an allogeneic ("off-the-shelf") CAR-T therapy, and T-cell receptor therapies in cancer.

Another major deal saw Celgene buy US-based Juno Therapeutics last year for \$9bn. Juno was at one point tipped to be first to market with a CAR-T therapy, but is now contenting itself with what it claims will be a safer and more effective offering, lisocabtagene maraleucel, in relapsed/refractory diffuse large B-cell lymphoma.

Smaller firms are clearly making their presence felt. The most recent firm to enjoy regulatory success, bluebird bio with Zynteglo, has a pipeline of *ex vivo* cell and gene therapies that span cancer and rare diseases with its expertise in lentiviral

vectors. It is aiming to commercialize CAR-T therapies against the novel BCMA target in collaboration with Celgene.

Other outfits include Sarepta Therapeutics, which is advancing a 14-candidate gene therapy pipeline, led by Phase II microdystrophin for DMD. It wants to be a leader in gene therapies for various types of muscular dystrophies.

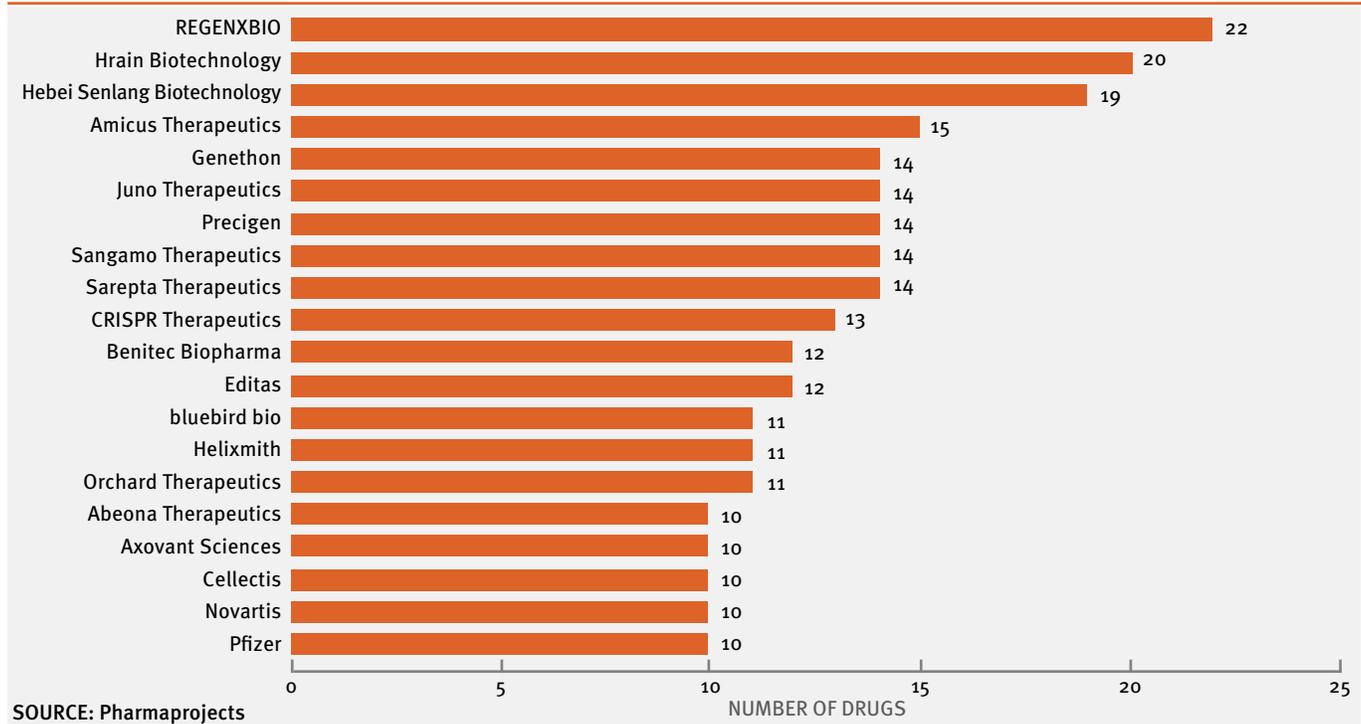
Currently, however, the company with the biggest gene therapy pipeline is specialist REGENXBIO Inc., with 22 gene therapies in development. It is taking a dual approach by developing an internal pipeline using its NAV AAV platform while licensing the technology to other players including Novartis (*see Exhibit 3*).

**Future Challenges**

The real challenge for these products is to prove themselves on the market: can they move from curiosities to cash cows?

Their development costs and manufacturing issues mean gene therapies do not come cheap and the field has not gotten off to an auspicious start commercially. The first western product, uniQure's Glybera, approved in the EU for lipoprotein lipase deficiency, flopped. Weak clinical efficacy plus a \$1m per treatment price tag meant it failed to get reimbursed nationally by any

### Exhibit 3 Most Active Gene Therapy Companies By Pipeline Size



European country and in the end only one patient was ever treated before uniQure decided against renewing its marketing authorization (it expired in 2017).

Amgen's Imlygic, the first approved gene therapy in the US, has struggled too and Datamonitor Healthcare analysts envision peak sales of only around \$175m in 2026.

Sales of the EU's first cell and gene therapy, Strimvelis, approved in 2016 for SCID, also withered in the face of an extremely small patient population and cross-country reimbursement issues as it could only be administered in single Italian clinic. GlaxoSmithKline always insisted it did not expect to make a profit from Strimvelis, rather it was looking to use the platform to build out further indications and to "familiarize stakeholders" with these types of therapies. It has now divested the product to Orchard Therapeutics.

The more recently approved CAR-Ts, Kymriah and Yescarta, have fared much better, becoming part of the standard of care for acute lymphoblastic leukemia and diffuse large B-cell lymphoma but still the sales are less than stellar. Kymriah's second-quarter 2019 revenues came in at just \$58m, only slightly up on \$45m in the first quarter. Yescarta,

meanwhile, brought in \$120m for Gilead in the same time period. Both companies insist they are confident in their longer-term trajectories.

But it is the newest arrivals, the one-time therapies for inherited disorders, Luxturna, Zolgensma and Zytiglo, with their pioneering pricing plans, that will really stress test the new field's commercial prospects.

Spark Therapeutics was first to suggest a five-year pricing model for its treatment for vision loss due to a genetic mutation in both copies of the *RPE65* gene, Luxturna (now licensed outside the US to Novartis), which it pitched at \$850,000 for both eyes.

Zynteglo is yet to launch following its first approval in the EU in June, but bluebird has put a price tag on it of €1.575m (\$1.78m), again spread over five years.

Novartis took pricing up another gear with Zolgensma, suggesting, upon its first approval in the US at the end of May, an annuity-like model under which Zolgensma would cost \$425,000 annually for five years. This makes it the world's most expensive drug with a total price tag of over \$2.1m, and with that kind of notoriety its performance will be key to sentiment. Novartis CEO Vas Narasimham says the

launch is going well but stayed mum during its second-quarter financial results presentation as to exactly how well.

Its performance, and that of its peers, could determine whether gene therapy will turn the corner as a commercial prospect, or whether failure here will mean a second Dark Age will descend. ❄️

IV12432

**Comments:**

Email the author: [Alex.Shimmings@Informa.com](mailto:Alex.Shimmings@Informa.com)

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##### Approved Gene Therapies Worldwide, July 2019

View our interactive data visualization which provides in-depth insight to the approved gene therapies throughout the world. <https://invivo.pharmaintelligence.informa.com/>

Read more on this topic in reports from Datamonitor Healthcare analyst Amanda Micklus:

- *Gene Therapy Pipeline and Portfolio Analysis*
  - *Gene Therapy Commercialization – Opportunities and Barriers*
- [Amanda.Micklus@informa.com](mailto:Amanda.Micklus@informa.com)

# On the Move

Recent executive appointments  
in the life sciences industry



■ ROBERT ANG



■ PRITI HEGDE



■ TERI LOXAM



■ JOHN LUNGER

## COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Jack Phillips	Accelerate Diagnostics Inc	Chief Operating Officer	Roche Diagnostics North America	Chief Executive Officer and President	8-Aug-19
Rafael Amado	Allogene Therapeutics	Chief Medical Officer and Executive Vice President, R&D	Adaptimmune	President, R&D	3-Sep-19
Scott Coiante	Aprea AB	Chief Financial Officer and Senior Vice President	Agile Therapeutics	Senior Vice President and Chief Financial Officer	5-Aug-19
Manish Wadhwa	BioTelemetry Inc	Chief Medical Officer	Geneva Healthcare Inc	Chief Medical Officer	5-Aug-19
Howie McKibbin	Botanix Pharmaceuticals	Chief Commercial Officer	Dermavant Sciences	Senior Vice President	1-Aug-19
Richard (Ric) Peterson	Botanix Pharmaceuticals	Chief Financial Officer	Dermavant Sciences	Chief Financial Officer	1-Aug-19
Carl J. St. Bernard	CeloNova BioSciences Inc	Chief Executive Officer and President	Tryton Medical	Chief Executive Officer and President	6-Aug-19
Theodore (Theo) Danoff	Complexa Inc	Chief Medical Officer	Clarus Therapeutics	Chief Medical Officer and Senior Vice President, Clinical and Medical Affairs	19-Aug-19
Andre Verwei	Cristal Therapeutics	Chief Financial Officer	Virtual BV	Managing Director	1-Aug-19
Janet Dorling	CymaBay Therapeutics	Chief Commercial Officer	Achaogen	Chief Commercial Officer	5-Aug-19
Simon King	Daiichi Sankyo Inc	Chief People Officer	Bristol-Myers Squibb	Global Head, Talent and Workforce Innovation	12-Aug-19
Priti Hegde	Foundation Medicine Inc	Chief Scientific Officer	Roche Genentech	Senior Director and Principal Scientist, Oncology Biomarker Development	1-Sep-19

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

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■ **ALEX MARTIN**



■ **RICHARD (RIC) PETERSON**



■ **EDWARD STEWART**



■ **ROGER TELL**

#### COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Maya Martinez-Davis	GlaxoSmithKline plc	President, US Pharmaceuticals	EMD Serono	Senior Vice President, Global Oncology	15-Sep-19
Shahin Fesharaki	Hikma Pharmaceuticals plc	Chief Scientific Officer and Global Head, Research and Development	Actavis	Chief Operating Officer, Global Research and Development	5-Aug-19
Anders Karlsson	Idogen AB	Chief Executive Officer	Allenex AB	Chief Executive Officer	19-Aug-19
Bams Abila	Immodulon Therapeutics Ltd	Chief Medical Officer	Cmed	Chief Medical Officer	8-Aug-19
Leslie McDonnell	IRadimed Corp	Chief Executive Officer, President and Director	Natus Medical	Vice President and General Manager	19-Aug-19
Matthew Call	iTeos Therapeutics SA	Chief Operating Officer	Endocyte	Chief Operating Officer	13-Aug-19
Fred Grossman	Mesoblast Ltd	Chief Medical Officer	Glenmark	Chief Medical Officer	12-Aug-19
Nicolas Leupin	Molecular Partners AG	Chief Medical Officer	argenx	Chief Medical Officer	1-Sep-19
Lars Nieba	Nordic Nanovector ASA	Chief Technology Officer	Bayer AG	Vice President and Strategic Product Lead	1-Dec-19
Kester Nahen	Notal Vision Ltd	Chief Commercial Officer	Heidelberg Engineering GmbH	Managing Director	8-Aug-19
Alex Martin	Palladio Biosciences	Chief Executive Officer	Realm Therapeutics	Chief Executive Officer	8-Aug-19
Eyal Rubin	Protalix Biotherapeutics	Chief Financial Officer and Senior Vice President	BrainStorm Cell Therapeutics	Chief Financial Officer and Executive Vice President	22-Sep-19

**COMPANY CHANGES**

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Cris Calsada	Regulus Therapeutics	Chief Financial Officer	Sanifit	Chief Financial Officer	30-Aug-19
Mikko Moilanen	Revenio Group Corp	Chief Executive Officer	Grano Group Oy	Chief Executive Officer	5-Aug-19
Edward Stewart	Ribon Therapeutics Inc	Chief Business Officer	Commense Inc	Chief Executive Officer and President	6-Aug-19
Sudha Parasuraman	Ribon Therapeutics Inc	Chief Medical Officer	X4 Pharmaceuticals	Chief Medical Officer	6-Aug-19
Ajim Tamboli	Rodin Therapeutics	Chief Financial Officer	Asymmetry Capital Management	Investor	6-Aug-19
Noah Nasser	Serimmune Inc	Chief Executive Officer	Human Longevity Inc	Chief Commercial Officer	6-Aug-19
Jorgen Wittendorff	Silence Therapeutics	Head, Manufacturing	Ablynx	Senior Director, CMC and Product Supply	5-Aug-19
Frank Perier	SpringWorks Therapeutics	Chief Financial Officer	Forest Laboratories Inc	Chief Financial Officer	15-Aug-19
Teri Loxam	SQZ Biotech	Chief Financial Officer	Merck & Co Inc	Senior Vice President, Investor Relations and Global Communications	7-Aug-19
Dan Chevallard	Viracta Therapeutics Inc	Chief Financial Officer	Regulus Therapeutics Inc	Chief Financial Officer, Vice President, Finance and Accounting and Vice President, Accounting and Financial Reporting	1-Aug-19
Robert Ang	Vor Biopharma Inc	Chief Executive Officer and President	Neon Therapeutics	Chief Business Officer	7-Aug-19
Mark Baldry	WAVE Life Sciences	Chief Commercial Officer	Amicus Therapeutics	Senior Vice President, Global Marketing and Commercial Operations	6-Aug-19

**PROMOTIONS**

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
Clifford B. Fleet	22nd Century Group Inc	Chief Executive Officer, President and Director	Strategic Advisor	3-Aug-19
John Lunger	Adaptimmune Therapeutics plc	Chief Patient Supply Officer	Senior Vice President, Manufacturing and Supply Chain	1-Aug-19
Michal Fresser	Axon Neuroscience SE	Chief Executive Officer, Axon Group	General Counsel	1-Aug-19
Aaron Mambrino	Dymax Corp	President, Dymax Americas	Global Chief Financial Officer	1-Aug-19
Domenic Ciarico	Endo International plc	Chief Commercial Officer, Sterile and Generics and Executive Vice President	Senior Vice President and General Manager, Par Sterile Products	1-Aug-19
Jyoti Mehra	Gilead Sciences Inc	Global Head, Human Resources	Vice President, Human Resources	1-Aug-19
Roger Tell	Isofol Medical AB	Chief Scientific Officer and Chief Medical Officer	Chief Scientific Officer	15-Aug-19

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
John Kozlowski	Lannett Co Inc	Chief Financial Officer	Chief of Staff and Strategy Officer	31-Aug-19
Ryan Zeidan	Millendo Therapeutics Inc	Chief Development Officer	Interim Chief Medical Officer and Senior Vice President, Development	20-Aug-19
Hyun-Jung Lee	Samyang Biopharmaceuticals Corp	President, Samyang Biopharm USA	Chief Strategy Officer	5-Aug-19
Reshma Kewalramani	Vertex Pharmaceuticals Inc	Chief Executive Officer and President	Chief Medical Officer	1-Apr-20

### DIRECTORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Anne Myong	Align Technology Inc	Director	1-Aug-19
Paul Meister	Amneal Pharmaceuticals Inc	Chairman	5-Aug-19
Werner Cautreels	Cristal Therapeutics	Director and Chairman, Supervisory Board	1-Aug-19
Andrew A.F. Hack	Dynavax Technologies Corp	Director	12-Aug-19
Howard Mayer	Entasis Therapeutics	Director	5-Aug-19
Kevin L. Lorenz	Fortress Biotech Inc	Director	19-Aug-19
Thomas Taapken	Imcyse	Executive Chairman	5-Aug-19
Amy L. Ladd	Intuitive Surgical Inc	Director	1-Aug-19
Olafur Ragnar Grimsson	Kerecis	Director	5-Aug-19
David Gill	Melinta Therapeutics Inc	Chairman	9-Aug-19
Lynne N. Ward	Merit Medical Systems Inc	Independent Director	19-Aug-19
Alfred Coats	Millar Inc	Chairman	20-Aug-19
James A. Datin	OraSure Technologies Inc	Director and Member, Audit and Compensation Committees	14-Aug-19
Maya R. Said	Pieris Pharmaceuticals Inc	Director	1-Aug-19
Bill Welch	Serimmune Inc	Director	6-Aug-19
Chris Nolet	Viela Bio	Director	19-Aug-19

### ADVISORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
David Briscoe	aTyr Pharma Inc	Scientific Advisor	6-Aug-19
Alan Korman	Dragonfly Therapeutics	Scientific Advisory Board Member	6-Aug-19
Sir Gregory Winter, FRS	Orion Biotechnology	Chairman, Scientific Advisory Board	5-Aug-19

# Deal-Making

Covering deals made August 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.

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## IN VITRO DIAGNOSTICS

### Financings

**Quanterix** brings in \$56.4m through FOPO

## MEDICAL DEVICES

### Mergers & Acquisitions

**AtriCure** buys **SentreHEART**

**Avedro, Glaukos** merge

**Hill-Rom** acquires wearable respiratory device maker **Breathe Technologies** for \$130m

**Siemens Healthineers** buys **Corindus Vascular** for \$1.1bn

**Stryker** boosts surgical device sterilization offerings through buy of **TSO3**

### Alliances

**Boston Scientific** to distribute **Endologix's** products in China

### Financings

**Apollo Endosurgery** enters into \$20m convertible debt financing

Israeli aesthetic device firm **InMode** nets \$65.1m in Nasdaq IPO

**Obalon** nets \$13.9m through public offering

Public offering nets \$42.3m for **Vapotherm**

## PHARMACEUTICALS

### Mergers & Acquisitions

**Aquinox** and **Neoleukin** merge to develop immunotherapies

**Bayer** buys cell therapy investment **BlueRock** for up to \$600m

Permira buys out CDMO **Cambrex** for \$2.47bn

**SWK Holdings** acquires **Enteris BioPharma** for \$21.5m, plus a share in future milestones and royalties

**Jazz** acquires neuro-focused **Cavion** for up to \$312.5m

**Zogenix** to pay \$250m up front and up to \$150m in earn-outs for **Modis Therapeutics**

### Alliances

**AZ** grants mAb rights to **Aevi Genomic**

**Celgene** divests **Otezla** to **Amgen** for \$13.4bn as condition of acquisition by **BMS**

**Bausch** sublicenses **Leo Pharma** ex-European rights to brodalumab

**Cara** licenses **Enteris' Peptelligence** to develop oral formulation of **Korsuva**

**Celgene** partners with **Immatics** for adoptive cell therapies

**Ultragenyx** co-develops **GeneTx's** GTX102; gains option to acquire company outright

**Paladin** to sell **Helsinn's** pracinostat in Canada

**Novartis** options **Iconic's** anti-TF ICON4 ophthalmology program

**Intellipharma** grants **Tris US** license to quetiapine ER

**Merck** enters vaccines pact with **Themis Bioscience**

**Newsoara** licenses rights to **Zenith's** BET inhibitor ZEN3694

**Pharming** gains exclusive worldwide license to **Novartis' CDZ173** for APDS

**Takeda** and **Sosei Heptares** pen GPCR alliance; initial target is GI diseases

### Financings

**Adamis** brings in \$11.3m through public offering

**Agile Therapeutics** brings in \$12.97m through FOPO

Upsized FOPO nets \$329m for **Allakos**

**Sobi** sells emapalumab PRV to **AstraZeneca** for \$95m

Public offering nets \$54m for **Bellicum**

**Bellicum** enters \$70m private placement agreement

**Clovis Oncology** nets \$254.8m in convertible senior notes sale

**Deciphera** nets \$376m through upsized public offering

Another preferred share sale nets \$8.6m for **Delcath**

**Dynavax** nets \$65.9m through public offering of common and preferred shares

**Ironwood** sells \$390m net amount of senior notes in upsized private offering

**MeiraGTx** nets \$70.7m through FOPO

**ObsEva** closes on \$25m of potential \$75m credit facility with Oxford Finance

Public offering nets \$212.6m for **Portola**

**SpringWorks** files for initial public offering

Public offering nets \$71.7m for **Stemline**

## IN VITRO DIAGNOSTICS

### FINANCINGS

#### QUANTERIX CORP.

**Quanterix Corp.** (digital immunoassay platforms for life sciences research and diagnostics) netted \$56.4m through the public sale of 2.4 million shares at \$25.25. The company plans to use the proceeds to expand its US and international life sciences commercial operations; improve its flagship *Simoa* bead-based protein detection technology and instruments to support the development of additional assays; fund development and potential regulatory approvals or clearances related to instruments, assay kits, and consumables outside of life science research; and pursue complementary acquisitions or business development opportunities. (Aug.)

Investment Banks/Advisors: Canaccord Genuity Inc.; JP Morgan & Co.; SVB Leerink

## MEDICAL DEVICES

### MERGERS & ACQUISITIONS

#### ATRICURE INC.

##### SENTEHEART INC.

**AtriCure Inc.** is paying \$40m up front in cash and stock to acquire closely held **SentreHEART Inc.** AtriCure could also hand over \$260m in earn-outs tied to SentreHEART's *Lariat* percutaneous left atrial appendage (LAA) closure device. (Aug.)

The earn-out payments, which are payable in cash and stock, would be as follows: \$140m related to the aMAZE IDE clinical trial, including PMA approval, and \$120m based on a reimbursement milestone for SentreHEART devices. *Lariat* has been FDA approved for soft-tissue closure in general surgery. The aMAZE trial is comparing LAA closure with *Lariat* plus a pulmonary vein isolation to ablation alone in patients with persistent atrial fibrillation. The *Lariat-RS* device for LAA exclusion to treat atrial fibrillation is already available in Europe where it is the only percutaneous LAA closure technology that permanently excludes the LAA without leaving a device in the heart over the long term. AtriCure offers the *Isolator Synergy Ablation* system, which is the only FDA-approved device for treating persistent atrial fibrillation. The

firm's *AtriClip* surgical left atrial appendage exclusion system for closure of the left atrial appendage in conjunction with other cardiac surgery procedures is complementary to the *Lariat* device. Fourteen-year-old SentreHEART has raised a total of \$69m in four venture rounds; investors include US Venture Partners, Prospect Ventures, Vivo Capital, and Decheng Capital.

#### GLAUKOS CORP. AVEDRO INC.

**Glaukos Corp.** is buying fellow public ophthalmic disease-focused firm **Avedro Inc.** in a stock swap. (Aug.)

Avedro shareholders will receive 0.365 shares of Glaukos stock for each share they own. The deal values Avedro at \$26.68 per share (a 42% premium) or a total acquisition value of \$500m. Post-transaction, Glaukos and Avedro will own 85%/15% of the combined company, respectively. Avedro went public earlier this year. Its *Corneal Remodeling Platform* uses corneal cross-linking to strengthen the cornea and modify its shape, which is effective as a treatment for progressive keratoconus in which the cornea thins and weakens over time. Corneal remodeling can also help to correct vision for healthy patients by reshaping the cornea through a non-invasive procedure. The platform incorporates Avedro's *XXL* and *Mosaic* systems, each of which delivers ultraviolet A light and bio-activated, single-use *Photrex* drug formulations to strengthen corneal tissue and halt progression of keratoconus. Avedro's product is the only FDA-approved therapy that can stop disease progression. The firm estimates the US market for the keratoconus therapy is around \$3bn. Avedro also has a pipeline of topical ophthalmics for refractive conditions, including presbyopia, low myopia, and post-cataract refractive error; the US market size for these therapies are estimated at about \$23bn. Glaukos' lead device candidate is the *iStent* implant that allows patients with glaucoma and cataracts to manage their intraocular pressure. FDA approval is anticipated for late 2020 or 2021. On the pharmaceutical side, the firm is developing *iDose* travoprost in Phase III trials for glaucoma. It expects to file for FDA approval in late 2021 or 2022. The acquisition combines two complementary hybrid ophthalmic pharmaceutical and device franchises thus providing

a cornerstone for Glaukos' new corneal health business. The deal comes just two months after Glaukos paid \$2.5m in cash plus up to \$45m in earn-outs for **Dose Medical**, a developer of micro-invasive, bio-erodible, sustained-release drug delivery platforms. In April 2019 Glaukos licensed exclusive US distribution rights to **Santen's** *MicroShunt* minimally-invasive ab-externo device for primary open-angle glaucoma. Glaukos expects to launch the product in 2020. Investment Banks/Advisors: Perella Weinberg Partners (Glaukos Corp.); Guggenheim Partners LLC (Avedro Inc.)

#### HILL-ROM HOLDINGS INC. BREATHE TECHNOLOGIES INC.

**Hill-Rom Holdings Inc.** agreed to acquire **Breathe Technologies Inc.** (wearable, non-invasive ventilation devices) in a transaction expected to close during Q4 2019. (Aug.)

Hill-Rom will pay \$130m in cash for the privately held company, which was founded in 2005 and has raised \$49m in venture financing since then. Breathe, which has annual revenues of about \$10m, designs and manufactures technologies to address respiratory and neuromuscular issues. Its flagship product is the *Life2000*, a volume-control, wearable, non-invasive mechanical ventilation system, which received FDA 510(k) clearance in June 2015. For use in the home or critical-care setting, the *Life2000* treats various medical conditions, including COPD, interstitial lung disease, and restrictive thoracic disorder, and assists with post-lung-transplant rehab. The addition of Breathe's *Life2000* offerings will enhance and complement Hill-Rom's existing non-invasive respiratory care portfolio, which includes the *Vest*, *VisiVest*, and *Monarch* wearable airway clearance systems.

#### SIEMENS HEALTHINEERS AG Siemens Medical Solutions USA Inc. CORINDUS VASCULAR ROBOTICS INC.

**Siemens Healthineers AG** and its **Siemens Medical Solutions USA Inc.** division are acquiring all issued and outstanding shares of **Corindus Vascular Robotics Inc.** for \$4.28 per share in cash (a 70% premium), for a deal value of \$1.1bn. (Aug.)

Corindus develops and sells devices for robotic-assisted coronary, peripheral,

and neurovascular procedures. Its *CorPath GRX* system is the first FDA-approved platform for interventional surgeons and is used for the remote delivery and manipulation of guidewires and catheters during surgical procedures. The technology allows the interventionalist to sit in a radiation-shielded cockpit in an effort to reduce radiation exposure while still remaining close to the patient during surgery. The company realized 2018 revenues of \$10.8m, of which \$8.6m was associated with *CorPath* sales. Siemens plans to integrate Corindus' technology with its own cardiovascular and neuro-interventional therapy systems.

#### STRYKER CORP. TSO3 INC.

**Stryker Corp.** agreed to acquire TSX-traded Canadian device company **TSO3 Inc.** (sterilization systems for surgical instruments). (Aug.)

Stryker will pay \$Cdn0.43 in cash per share (an 18% premium), for an enterprise value of \$Cdn68.4m (\$51.7m), including debt. TSO3 was founded in 1998 and specializes in low-temperature sterilization equipment, processes, and services for surgical instruments. Its suite of *Sterizone* products (and related consumable supplies and accessories) are applied to the sterilization of tools used in general surgical, gastrointestinal (including colonoscopes, gastroscopes, and duodenoscopes), and other procedures. TSO3's *Sterizone VP4* sterilizer was FDA approved in 2014 followed by clearances in Canada in 2015 and Europe in 2016. The low-temperature system uses vaporized hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and ozone (O<sub>3</sub>) as its sterilants for the reprocessing and terminal sterilization of heat- and moisture-sensitive metal and non-metal reusable devices. TSO3 primarily targets surgeons, endoscopists, OR directors, reprocessing and central sterilization, infection control, risk management, and purchasing departments of acute care and ambulatory care centers. Because of its compatibility with over 3.7k devices, the *Sterizone* line will likely be well suited to use for the instruments portfolio of Stryker's medical and surgical equipment unit. Investment Banks/Advisors: Piper Jaffray & Co. (TSO3 Inc.)

#### ALLIANCES

##### BOSTON SCIENTIFIC CORP. ENDOLOGIX INC.

Under a long-term collaboration, **Endologix Inc.** licensed **Boston Scientific Corp.** exclusive rights to distribute its products in China. (Aug.)

Boston Scientific's rights extend to Endologix's products for endovascular aneurysm repair (EVAR) and endovascular aneurysm sealing (EVAS), in addition

to the right of first negotiation for future products. Specific devices include the FDA-approved and CE-marked minimally invasive *Ovation iX* abdominal stent graft and *AFX2* endovascular abdominal aortic aneurysm (AAA) system. The *Ovation* endovascular device is delivered via catheter to treat AAAs. The stent graft is comprised of an aortic body section, two iliac limbs, and iliac extensions. *AFX2* integrates anatomical fixation with an advanced delivery system and graft material technology to treat AAAs. Boston Scientific will build a sales team to focus on selling Endologix's products, and Endologix will provide the firm with commercial and clinical support and training. Following regulatory approval, an initial product launch is expected in 2021. China is a key market for EVAR and Endologix chose to partner with Boston Scientific because of its expertise in vascular diseases.

#### FINANCINGS

##### APOLLO ENDOSURGERY INC.

**Apollo Endosurgery Inc.** (minimally invasive devices for bariatric and gastrointestinal procedures) entered into a \$20m private placement of unsecured convertible debt with accredited and institutional investors as well as officers and affiliates of certain directors of the company. The debentures are payable semi-annually at a rate of 6% per annum and convert into common stock at \$3.25 per share. (Apollo's stock averaged \$2.73 at the time of the sale.) (Aug.)

Investment Banks/Advisors: Craig-Hallum Inc.

##### INMODE LTD.

Israeli device firm **InMode Ltd.** (minimally invasive surgical aesthetics) netted \$65.1m through its initial public offering on Nasdaq of 5 million ordinary shares at \$14, the low end of its anticipated \$14-16 range. (Aug.)

Investment Banks/Advisors: Barclays Bank PLC; Canaccord Genuity Inc.; Robert W. Baird & Co. Inc.; UBS Investment Bank

##### OBALON THERAPEUTICS INC.

**Obalon Therapeutics Inc.** (developer of the only FDA-approved swallowable, gas-filled intragastric balloon system for obesity) netted \$13.9m through a follow-on public offering of 2 million common shares at \$4 and 1.7 million pre-funded warrants to purchase one common share at \$3.999. The company also issued five-year warrants to buy another 1.5 million common shares at an exercise price of \$4.40. (Aug.)

Investment Banks/Advisors: Alliance Global Partners

##### VAPOTHERM INC.

**Vapotherm Inc.** (develops and sells its *Hi-VNI* ventilatory support systems to treat respiratory distress) netted \$42.3m through a public offering of 3.1 million

shares at \$14.50. Proceeds will be used to hire additional sales and marketing staff, expand US and international marketing efforts, and support continued R&D. (Aug.)  
Investment Banks/Advisors: BTIG LLC; Bank of America Merrill Lynch; Canaccord Genuity Inc.; William Blair & Co.

## PHARMACEUTICALS

### MERGERS & ACQUISITIONS

#### AQUINOX PHARMACEUTICALS INC. NEOLEUKIN THERAPEUTICS INC.

Public Vancouver-based biotech **Aquinox Pharmaceuticals Inc.** acquired **Neoleukin Therapeutics Inc.** (de novo protein design technology for cancer drug development) in a reverse merger through which Aquinox will assume the Neoleukin name and Neoleukin's executive staff. (Aug.)

Under terms of the deal, Aquinox acquired all of the outstanding capital stock of Neoleukin in exchange for 4.6 million newly issued Aquinox common shares (representing approximately 19.5% of the voting power of Aquinox prior to the deal), and shares of Aquinox convertible preferred stock convertible into a total of 10.2 million shares of Aquinox common stock. Aquinox shareholders come out owning about 61.42% of the combined entity and former Neoleukin stockholders will own 38.58%. Headquarters will be located in Seattle, Washington (Neoleukin's original home), and the company's stock has been reassigned a new ticker, NLTX. Aquinox struggled ahead of the acquisition announcement, dropping its lead inflammatory pain candidate following a Phase III failure. The merged entity comes out of the gate with capitalization of \$65m to support development and commercialization of former Neoleukin's computationally-designed protein therapies for inflammation, autoimmune conditions, and immunoncology. Lead project NL201 (originated at the **University of Washington**, which spun out Neoleukin at the beginning of 2019) is a CD25-independent IL-2/IL-15 agonist immunotherapy approaching IND-enabling studies for cancer. The company will develop additional cytokine mimetics (which it calls *Neoleukins*) for additional cancers as well as autoimmune and allergic diseases. Investment Banks/Advisors: SVB Leerink (Aquinox Pharmaceuticals Inc.); MTS Health Partners (Neoleukin Therapeutics Inc.)

#### BAYER AG BLUEROCK THERAPEUTICS

**Bayer AG** fully acquired privately held cell therapeutics developer **BlueRock Therapeutics**, paying \$240m in cash up front for 59.2% of the company it did not already own, and pledging another \$360m in development milestones. Including

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Bayer's previous investment, BlueRock is valued at \$1bn. (Aug.)

BlueRock, a 2016 start-up founded around stem cell technology developed at **Kyoto University**, launched with a massive \$225m series A round from Bayer (Leaps by Bayer) plus Versant Ventures. BlueRock's **CELL+GENE** platform enables differentiation of universal pluripotent stem cells into allogeneic cell therapies, which can additionally be genetically engineered so that they can produce enzymes, antibodies, or other types of therapeutic proteins. The company is focused on neurology, cardiology, and immunology, and has lead candidates in the pipeline for Parkinson's disease (dopaminergic neuron therapy in preclinical testing, with Phase I planned for 2019) and heart failure (cardiomyocyte in preclinical). In immunology, areas of interest include fibrosis and graft vs. host disease. BlueRock has several collaborations, including with the **McEwen Centre for Regenerative Medicine**, **University Health Network**, and **VistaGen** in the cardiovascular area. Earlier this year, BlueRock and **Editas Medicine** cross-licensed their technologies with the goal of producing allogeneic pluripotent stem cell lines based on Editas' CRISPR gene editing and BlueRock's induced pluripotent stem cell platform. The BlueRock acquisition marks Bayer's third major investment in regenerative medicine in recent years. In 2014 it gained exclusive rights to a hemophilia A gene therapy from Dimension Therapeutics (now part of **Ultragenyx Pharmaceutical**), in an alliance worth \$252m. And in 2015, Bayer and **CRISPR Therapeutics** established the joint venture **Casebia** to develop CRISPR gene editing therapies in blood disorders, blindness, and congenital heart disease.

#### CAMBREX CORP.

An affiliate of the investment firm Permira agreed to acquire public contract development and manufacturing organization (CDMO) **Cambrex Corp.** (small-molecule drug manufacturing and analytical testing services). Already approved by the company's board, the transaction is expected to close during Q4 2019. Cambrex is entitled to solicit other acquisition proposals from third parties during a 45-day go-shop period. (Aug.)

Cambrex shareholders will receive \$60 in cash (a 39% premium) for each outstanding share; including the company's \$445m in net debt, the transaction is valued at \$2.47bn. Permira will fund the transaction through equity and debt from outside sources, including debt financing from RBC Capital Markets. Cambrex, which was founded in 1981, has over the years built up its capabilities across the entire drug lifecycle through acquisitions including, most recently, **Halo Pharma**

(finished dosage form CDMO) in 2018 and **Avista Pharma Solutions** (early-stage API and drug product development, cGMP manufacturing, stand-alone analytical microbiology testing, and solid-state sciences) earlier this year. Cambrex currently operates within three segments: drug substance (DS; custom development and manufacture of APIs and intermediates), drug product (DP; contract development and commercial manufacturing of finished dosage forms including oral solids, liquids and creams, and sterile and non-sterile ointments), and early-stage development and testing (ESDT; a combination of analytical testing, early-stage process chemistry, formulation development, manufacturing, and solid state chemistry services). The DS segment is mostly the legacy Cambrex API business, and the DP unit includes the former Halo business, while ESDT is mostly comprised of the former Avista business. For the six months ended June 30, 2019, these three together reported revenues of \$336.3m, with the DS unit accounting for about 72% of that amount. Investment Banks/Advisors: Morgan Stanley & Co.

#### ENTERIS BIOPHARMA INC.

SWK Holdings Corp. acquired private US-based drug delivery firm **Enteris BioPharma Inc.** (technology enabling injectable to oral conversion of peptides and difficult-to-formulate small molecules) from fellow investment firm Victory Park Capital. (Aug.)

SWK paid \$21.5m at closing and will receive a percentage of the milestone and royalty payments associated with a separate licensing deal Enteris signed earlier this month with **Cara Therapeutics** (which gained Enteris' **Peptelligence** drug delivery technology to develop an oral formulation of Cara's **Korsuva** (difelikefalin) for pruritus) as well as a share in other future licensing deals. In the Cara alliance, Enteris is receiving \$8m up front; undisclosed development, regulatory, and commercialization milestones; and low-single-digit royalties on net sales. Under the current acquisition agreement, SWK is entitled to future payments under the Cara alliance as follows: 60% of the first milestone, 25% of any remaining milestone and royalty payments until an aggregate \$32.75m is reached, and all proceeds after that split evenly between Enteris and SWK, which expects this portion to be greater than the purchase price. As a wholly owned stand-alone subsidiary of SWK, Enteris will retain its current management team and continue to focus on its development of its 505(b)(2) regulatory pathway pipeline--including Phase II **Ovarest** (leuprolide), an oral peptide for endometriosis; **Tobrate** (tobramycin), an oral tablet in Phase I for uncomplicated urinary tract infections; and a preclinical octreotide oral tablet formulation for neuroendocrine tumors--as well as external

partnerships surrounding its **Peptelligence** technology. If Enteris' **Ovarest** and **Tobrate** are out-licensed, SWK will receive 40% of any license or sales proceeds until Enteris reaches \$3m on each asset, with SWK receiving a 70% interest after that. If Enteris' octreotide is out-licensed, SWK will receive 90% of any license or sales proceeds. SWK will retain 100% of any manufacturing-related revenue related to all three potential products. SWK believes near- to medium-term licenses could exceed \$50m.

#### JAZZ PHARMACEUTICALS PLC CAVION INC.

**Jazz Pharmaceuticals PLC** agreed to acquire private US-based **Cavion Inc.** (therapeutics for chronic and rare neurological diseases) through a merger with a Jazz subsidiary. (Aug.)

The company was founded in 2005 as Tau Therapeutics, a **University of Virginia** spin-out initially focused on cancer. In 2014, Tau merged with CNS company Xdynia, and was renamed Cavion. In the current transaction, Jazz will provide \$52.5m up front as well as potential earn-outs up to \$260m based on the achievement of certain clinical (\$30m), regulatory (\$45m), and commercialization (\$185m) milestones tied to Cavion's T-type calcium channel modulator pipeline, led by Phase II CX8998 for essential tremor (ET). Jazz will also provide sales-based tiered royalties to **Merck & Co.**, from which Cavion licensed CX8998 under a previously undisclosed deal. In the ET indication (for which CX8998 has a 20% likelihood of approval, 3% above average), Cavion announced Phase II proof-of-concept results in October 2018, with a Phase II clinical study in Parkinson's-associated ET expected to begin next year. The candidate is also development for other indications such as epilepsy (Phase II) and chemotherapy-induced peripheral neuropathy (preclinical). The acquired company's CX8998, two CNS candidates, and one undisclosed compound will boost and complement Jazz's heavily neurology-focused R&D pipeline, headed up by Phase III narcolepsy compound JZP258 (for which an NDA filing is expected later this year). Also for narcolepsy, Jazz's **Sunosi** (solriamfetol) was launched in the US just last month. Jazz also boosted its cancer assets with a potential \$206.5m July 2019 deal in-licensing **Redx Pharma's** pan-RAF inhibitor program. Investment Banks/Advisors: MTS Health Partners (Cavion Inc.)

#### ZOGENIX INC. MODIS THERAPEUTICS INC.

**Zogenix Inc.** is paying of \$175m in cash and \$75m in common stock to acquire fellow rare disease drug developer **Modis Therapeutics Inc.** Zogenix could also shell out \$150m in regulatory milestones tied to MT1621. (Aug.)

Modis's lead program MT1621 is a deoxynucleoside substrate enhancement therapy for thymidine kinase 2 deficiency (TK2d), which is a genetic mitochondrial DNA depletion disorder that mostly affects children and is often fatal. Concurrent with the acquisition, Modis announced positive results from the Phase II RETRO study. In addition to demonstrating a clinical benefit, MT1621 was generally safe and well-tolerated. The potential therapy currently has breakthrough designation in the US (February 2019) and priority medicines designation in Europe (November 2018). Specific terms of the earn-out payments are \$100m upon FDA approval of MT1621 and \$50m upon approval in Europe. In addition, Zogenix will pay a 5% sales royalty on MT1621; the royalty term expires on a country-by-country basis upon the later of 15 years after the first commercial sale of MT1621. Modis' compound will fit nicely with Zogenix's Phase III *Fintepla* (fenfluramine; formerly known as ZX008) for Dravet syndrome and Lennox-Gastaut syndrome, which are rare childhood-onset epilepsies. Zogenix is now well-positioned to become a leader in the rare disease space. Investment Banks/Advisors: SVB Leerink (Zogenix Inc.)

## ALLIANCES

### AEVI GENOMIC MEDICINE INC. ASTRAZENECA PLC

**AstraZeneca PLC** granted **Aevi Genomic Medicine Inc.** an option to license exclusive global rights to develop and sell its Phase II-ready monoclonal antibody MEDI2338. (Aug.)

MEDI2338, an interleukin-18 antagonist, was in trials for COPD and post-acute coronary syndrome patients before AZ halted development due to lack of efficacy. If Aevi satisfies conditions (securing additional funding), it will license the candidate with plans to develop it for adult onset Still's disease (AOSD), a rare and orphan rheumatological disease that causes symptoms including daily fever, rash, and arthritis, with common complications such as splenomegaly, heart, and liver disease. If Aevi exercises the option, it will pay a combined mid-single-digit millions in cash and equity up front (*Strategic Transactions* estimates \$5m), up to \$162m in development and sales milestones, and tiered low double-digit royalties (estimated range of 10-29%). The company could choose to develop MEDI2338 for other rare autoinflammatory diseases driven by IL-18 following its initial work in AOSD. The deal is the second in under a month for Aevi. In July, it licensed global rights to the mTOR inhibitor ASP7486 from **Astellas**. That project was originally eyed for development as a cancer therapy, but Aevi will explore the candidate's potential as a treatment for congenital lymphatic malformations.

### AMGEN INC. CELGENE CORP.

To satisfy FTC conditions to allow **Bristol-Myers Squibb Co.**'s \$74bn acquisition of **Celgene Corp.** to finalize, Celgene divested its blockbuster drug *Otezla* (apremilast) to **Amgen Inc.** for \$13.4bn (or about \$11.2bn net of the present value in anticipated future cash tax benefits). (Aug.)

Amgen gets *Otezla* and related intellectual property, including any patents that primarily cover apremilast and *Otezla*-related assets and liabilities. Certain Celgene employees dedicated to the drug will transfer to Amgen. BMS plans to use proceeds from the sale to reduce debt. The divestiture was first announced back in June but the specific third party on the deal was not disclosed. Investors were surprised by the news because BMS and Celgene don't have a significant amount of overlap in the immunology space. *Otezla* is approved for moderate-to-severe plaque psoriasis, psoriatic arthritis, and adults with oral ulcers associated with Behçet's disease; it is approved in 54 countries and generated \$1.61bn in 2018. In the US *Otezla* has patent protection through 2028. Industry analysts have forecasted the drug will reach around \$2.5bn in sales in 2023. Amgen says that apremilast complements its portfolio of psoriasis and inflammation therapies--especially *Enbrel* and *Amgevita*--and offers an alternative to the firm's biologics. (It is the only oral, non-biologic treatment for psoriasis and psoriatic arthritis.) BMS's acquisition of Celgene is now expected to close by the end of 2019.

### BAUSCH HEALTH COMPANIES INC. LEO PHARMA AS

**Bausch Health Ireland Ltd.** sublicensed **Leo Pharma AS** ex-European marketing rights to its (brodalumab) for moderate-to-severe psoriasis. (Aug.)

Under a 2015 deal with **AstraZeneca**, Bausch holds the worldwide rights, excluding Asia (where it's marketed by **Kyowa Kirin**) through its own 2015 partnership with AZ) and Europe (where Leo already has rights through a July 2016 alliance with AZ) Through the 2016 deal, Leo gained a European license to brodalumab in dermatology indications (along with global rights to atopic dermatitis mAb tralokinumab). In July 2017, Leo received marketing approval in Europe for *Kyntheum*, the name which brodalumab is marketed in that territory. In the current deal, Bausch, which markets the drug as *SILIQ*, will retain rights for the US and Canada. The additional territories give Leo the opportunity to address a significantly high unmet need in countries including Australia, Brazil, Egypt, Mexico, Russia, and Saudi Arabia.

### CARA THERAPEUTICS INC. ENTERIS BIOPHARMA INC.

**Enteris BioPharma Inc.** granted **Cara Therapeutics Inc.** a non-exclusive worldwide license (excluding Japan and South Korea) to its *Peptelligence* drug delivery technology to use in the development, manufacture, and commercialization of Cara's oral *Korsuva* (difelikefalin; CR845), a long-acting synthetic peptide peripheral kappa opioid receptor (KOR) agonist. (Aug.)

An oral formulation of *Korsuva* is currently in three Phase II trials for pruritus in patients with hepatic impairment due to primary biliary cholangitis (initiated in June 2019), stage III-V chronic kidney disease (CKD; initiated in 2018), and atopic dermatitis (initiated last month). An injectable formulation is in Phase III. Enteris' *Peptelligence* technology increases the solubility and absorption of both peptides and small molecules, while reducing variability and food effects. The *Peptelligence* enteric-coated tablet formulation is composed of a surfactant permeation enhancer that also acts as a solubilizing agent and citric acid, which acts as a calcium chelator to lower pH and increase absorptive flux. In exchange for the license, Cara will pay Enteris \$8m up front (half in cash and the other half through the issuance of 171k Cara common shares at \$23.42); development, regulatory, and commercialization milestones; and low-single-digit royalties on net sales within the licensed territory. For the first two years Cara has the right, under certain conditions, to buy out the royalty obligation for a lump sum in cash or 50% in cash and the remainder in additional Cara shares. Under a May 2019 agreement, Cara granted **Vifor Fresenius** exclusive worldwide development and commercialization rights (except in the US, Japan, and South Korea) to the injectable version of *Korsuva* for CKD-associated pruritus in dialysis patients.

### CELGENE CORP. IMMATICUS BIOTECHNOLOGIES GMBH

**Celgene Corp.** and **Immatics Biotechnologies GmbH** partnered to develop adoptive cell therapies for cancer. (Aug.)

Immatics uses its *XPRESIDENT* high throughput platform to identify target HLA peptides expressed the surface of tumor cells and not on the cell surface of normal tissue, and then uses T-cell receptors (TCRs) identified with the *XCEPTOR* TCR discovery and engineering program. The company is responsible for developing and validating any programs against the TCR targets it discovers for Celgene through the lead candidate stage. Celgene has options to license up to three targets; if exercised, it would then take over global development, manufacturing, and com-

mercialization, with Immatics retaining co-development or co-funding rights for certain therapies. Financial terms of the deal include a \$75m up-front payment to Immatics and up to \$505m per target in option exercise payments and milestones, plus tiered royalties. In an interview with *Scrip*, Immatics notes that the deal marks the first time the company has retained co-development and co-funding options, as its other deals have primarily been licensing transactions. It is also the company's first cell therapy partnership, and brings the firm its largest ever up-front payment. Celgene penned the deal amid its pending \$74bn takeover by **BMS**, continuing to strengthen its offerings in the cell therapy space.

**FOUNDATION FOR ANGELMAN SYNDROME THERAPEUTICS**

*GeneTx Biotherapeutics LLC*

**ULTRAGENYX PHARMACEUTICAL INC.**

**Ultragenyx Pharmaceutical Inc.** and **GeneTx Biotherapeutics LLC** agreed to collaborate on the development of GeneTx's GTX102 antisense oligonucleotide (ASO) for Angelman syndrome (AS), a rare neurogenetic disorder. (Aug.)

Launched early last year, GeneTx was founded by the non-profit patient advo-

cacy and research organization **Foundation for Angelman Syndrome Therapeutics** (FAST; its majority owner) and uses ASO technology exclusively licensed from **Texas A&M University** through a December 2017 deal. A debilitating neurological disorder, AS is caused by the mutation of the maternally inherited E3 ubiquitin ligase (UBE3A) gene. GTX102 has demonstrated in in vitro studies the ability to reactivate expression of the paternal UBE3A allele in neurons of the CNS, improving some of the symptoms associated with the condition. As part of the current tie-up, Ultragenyx may acquire GeneTx outright, paying \$20m up front for the exclusive option, which may be exercised any time prior to 30 days following FDA acceptance of the IND for GTX102, which is expected in 1H 2020. If Ultragenyx chooses to extend the option period until the earlier of 30 months from the first dosing of a patient in a planned Phase I/II study in AS or 90 days after those study results are available, it must pay an additional \$25m. During the exclusive option period, Ultragenyx will provide staff support, strategic guidance, and clinical expertise, while GeneTx will contribute its regulatory and scientific expertise and fund all development. The partners will collaborate on the IND sub-

mission and together manage the Phase I/II study. If Ultragenyx decides to exercise its option, it will pay an initial purchase price as well as contingent milestones and royalties and it becomes responsible for funding all GTX102 development and commercialization activities.

**HELSINN GROUP ENDO INTERNATIONAL PLC**

*Paladin Labs Inc.*

**Helsinn Group** granted **Endo Ventures Ltd.**'s **Paladin Labs Inc.** exclusive rights to sell the blood cancer candidate **pracinostat** in Canada following regulatory approval. (Aug.)

**Pracinostat**, an HDAC inhibitor, is in Phase III trials in combination with azacitidine for newly diagnosed acute myeloid leukemia patients who cannot undergo intensive chemotherapy. It is also in Phase II for treatment naïve high or very high-risk myelodysplastic syndrome. Helsinn will retain international development rights and supply the finished product to **Paladin**. Helsinn originally gained rights to **pracinostat** from **MEI Pharma** and last year granted **Menarini** exclusive global rights (excluding the US, Canada, Japan, and South America).

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## ICONIC THERAPEUTICS INC. NOVARTIS AG

**Iconic Therapeutics Inc.** granted **Novartis AG** an option on its **ICON4** ophthalmology program. (Aug.)

In exchange, Novartis made an up-front payment and an equity investment in Iconic. **ICON4**, currently in preclinical IND-enabling studies for age-related macular degeneration (AMD), is a monoclonal antibody that targets tissue factor (TF; a naturally occurring protein that plays a role in the coagulation cascade). Over-expression of TF causes inflammation and angiogenesis. Icon's TF approach has demonstrated early clinical validation and potential in various conditions, including retinal disease and cancer. **ICON4** specifically addresses TF overexpression in macular degeneration with an aim to improve patients' visual acuity, modify disease progression, and offer more efficacy and durability of effect than current AMD treatments. Clinical trials are expected to begin next year. Back in May, Exelixis optioned rights to Iconic's **ICON2** antibody-drug conjugate--another preclinical candidate that targets TF--in development for solid tumors.

## INTELLIPHARMACEUTICS INTERNATIONAL INC. TRIS PHARMA INC.

**Intellipharmaceuticals International Inc.** granted **Tris Pharma Inc.** exclusive US marketing, sales, and distribution rights to its quetiapine fumarate extended-release (ER) tablets, a generic equivalent to **AstraZeneca's Seroquel XR** marketed schizophrenia drug. The license includes the 50, 150, 200, 300, and 400 mg strengths. The partners also entered a concurrent commercial supply agreement. (Aug.)

Intellipharmaceuticals' generic quetiapine ER received ANDA approval from the FDA in May 2017 for schizophrenia, bipolar disorder, and major depressive disorder. Intellipharmaceuticals incorporates into various oral solid dosage drugs its *Hypermatrix* controlled-release platform that works within the body's gastrointestinal tract to deliver an active drug that has been imbedded in a homogeneous core and/or coatings consisting of one or more polymers that affect release rate at the specific time and according to the desired profile. The current deal enhances Tris' generics portfolio, which includes over 20 immediate- and extended-release dosage forms across multiple disease areas such as ADHD, pain, hypertriglyceridemia, asthma, and cough-cold.

## MERCK & CO. INC. THEMIS BIOSCIENCE GMBH

**Merck & Co. Inc.** has teamed up with **Themis Bioscience GmbH** to use Themis' measles virus vector platform to research

and develop vaccines against an undisclosed target. (Aug.)

The deal calls for researching funding to be provided by Merck, which will also make an equity investment in Themis. Merck could also pay up to \$200m in development and sales milestones, plus royalties, in exchange for exclusive rights. Themis' vector technology was originally developed by **Institut Pasteur** and later licensed to Themis. The platform has the capacity to incorporate multiple large recombinant protein antigens and deliver the antigens directly to macrophages and dendritic cells to trigger a specific immune response. Merck did not disclose a specific target for the deal, but Themis notes that it is working on an in-house vaccine for chikungunya, which it is advancing into Phase III studies.

## NEWSOARA BIOPHARMA CO. LTD. ZENITH EPIGENETICS LTD.

**Zenith Epigenetics Corp.** granted **Newsara BioPharma Co. Ltd.** rights to develop, market, and distribute its BET inhibitor **ZEN3694** in China, Hong Kong, Taiwan, and Macau. (Aug.)

**ZEN3694** is in Phase II trials for metastatic castration-resistant prostate cancer and triple-negative breast cancer; Newsara's rights cover all indications. The company will pay \$15m in up-front and near-term development milestone payments; up to \$63m in sales milestones; and royalties up to 6%. Newsara was formed last year to in-license pharma projects for development and commercialization in the Asia Pacific/China region. Its pipeline also includes **Vtv Therapeutics'** **HPP737**, a PDE4 inhibitor in Phase I trials for asthma and COPD and in preclinical studies for psoriasis; Newsara licensed rights in May 2018 covering development and sale of the candidate in China, Hong Kong, Macau, Taiwan, Thailand, Vietnam, Indonesia, Malaysia, Philippines, Singapore, Myanmar, Cambodia, Laos, Brunei, and South Korea.

## NOVARTIS AG PHARMING GROUP NV

**Pharming Group NV** agreed to exclusively develop and commercialize **Novartis AG's** **CDZ173** (leniolisib), for activated phosphoinositide 3-kinase delta syndrome (APDS), an ultra-rare immune disease. (Aug.) Pharming will pay \$20m up front, regulatory and commercial milestones, plus tiered, double-digit royalties on net sales. **CDZ173** is a small-molecule phosphoinositide 3-kinase (PI3K) delta inhibitor in Phase II/III for APDS, an immune deficiency caused by a mutation in the PIK3CD gene that causes over activity of the PI3 kinase pathway in the immune system. Pharming will join Novartis to complete enrollment in clinical sites in

the US and Europe for the ongoing registration-enabling trial and the open label extension study. If approved, Pharming will commercialize **CDZ173** through its existing US and European sales channels and investigate the best way to promote it in other regions worldwide. The candidate is expected to reach the market in 2H 2021 or 1H 2022. Pharming indicates that there is already a commercially available companion diagnostic able to identify the patients with the PIK3CD mutation who will benefit from **CDZ173**. The addition of **CDZ173** could potentially boost Pharming's rare disease portfolio to two products; it currently includes just one other drug, recombinant human C1 esterase inhibitor **Ruconest** (conestat alfa) for acute hereditary angioedema (approved in 2014).

## SOSEI HEPTARES TAKEDA PHARMACEUTICAL CO. LTD.

**Sosei Heptares** penned the second agreement in a month involving its **STaR** GPCR technology, this time with **Takeda Pharmaceutical Co. Ltd.** with an initial focus on small-molecule and biologics drug discovery for gastrointestinal diseases. (Aug.)

Takeda will nominate multiple GPCR targets to which Sosei will apply **STaR**, its platform that engineers functional, stabilized GPCRs. During the multi-year agreement, Sosei gets \$26m in up-front and near-term payments; research funding; and development, commercialization, and net sales milestones that could exceed \$1.2bn, plus royalties. Takeda comes out of the deal with exclusive global rights to any resulting compounds. Last month, Sosei signed a similar agreement with **Roche's Genentech** in which the companies will explore GPCR modulators for several undisclosed disease targets. In that collaboration, Sosei is also eligible for \$26m in up-front and near-term monies, as well as over \$1bn in total milestones.

## FINANCINGS

### ADAMIS PHARMACEUTICALS CORP.

**Adamis Pharmaceuticals Corp.** netted \$11.3m through a public offering of 12 million common shares at \$1. Investors also received five-year warrants to purchase 12 million shares at \$1.15. The company is developing treatments for allergies, asthma, and opioid overdose, and will use the offering proceeds for corporate needs including R&D expenses, manufacturing, personnel costs, and the purchase of new technologies or products. (Aug.)

Investment Banks/Advisors: Maxim Group LLC; Raymond James & Associates Inc.

### AGILE THERAPEUTICS INC.

**Agile Therapeutics Inc.** (women's health) netted \$12.97m in a public offering of

14.5 million shares (including the over-allotment) at \$0.95 each. The company will use the proceeds to support US commercialization of *Twirla* (AG20015), its once-weekly hormonal contraceptive patch; development of other candidates; and investments in or acquisitions of complementary businesses or technologies. Agile resubmitted an NDA for *Twirla* in May 2019 to address concerns in a complete response letter issued by the FDA in December 2017 that identified potential problems with *in vivo* adhesion properties and manufacturing; it has a PDUFA date of November 16, 2019. (Aug.)

Investment Banks/Advisors: HC Wainwright & Co.; Oppenheimer & Co. Inc.

#### ALLAKOS INC.

Therapeutic antibody developer **Allakos Inc.** netted \$329m through an upsized public offering of 4.5 million common shares at \$77. (The company originally filed to sell \$200m of its shares.) Allakos is developing lead Siglec-8 targeting antibody AK002 in Phase I and Phase II trials for eosinophil-driven diseases, with an initial focus on eosinophilic gastritis (Phase II). (Aug.)

Investment Banks/Advisors: Goldman Sachs & Co.; Jefferies & Co. Inc.; LifeSci Capital LLC; William Blair & Co.

#### ASTRAZENECA PLC

##### SWEDISH ORPHAN BIOVITRUM AB

**Swedish Orphan Biovitrum AB** (Sobi) sold **AstraZeneca PLC** a Priority Review Voucher for \$95m. Sobi gained the PRV when it acquired **Novimmune SA's** emapalumab business in June of this year. It is not clear what AZ's intentions are for the PRV; emapalumab is indicated for pediatric and adult patients with primary haemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or intolerance to conventional HLH therapy. (Aug.)

#### BELLICUM PHARMACEUTICALS INC.

**Bellicum Pharmaceuticals Inc.** (cellular immunotherapies for cancer and orphan blood diseases) netted \$54m through a public offering of 575,000 series 1 redeemable convertible preferred shares (each converts into 100 common) priced at \$100 apiece. Investors also received seven-year warrants to purchase 57.5 million common shares at \$1.30. Concurrent with the public offering, Bellicum entered into agreements with certain investors for a future private placement of up to \$70m of the company's series 2 and series 3 preferred shares, together with common stock purchase warrants. The placement would occur in two or more tranches. (Aug.)

Investment Banks/Advisors: Jefferies & Co. Inc.; Ladenburg Thalmann & Co. Inc.; Wells Fargo Securities LLC

#### BELLICUM PHARMACEUTICALS INC.

**Bellicum Pharmaceuticals Inc.** (controllable cell therapies) entered into a private placement agreement with institutional investors for the sale of up to \$70m of the company's series 2 and series 3 preferred shares, along with common share purchase warrants (50k series 2 redeemable convertible non-voting preferred shares at \$100 each and warrants to purchase up to 28 million common at \$1, and 250k series 3 redeemable convertible non-voting preferred shares at \$140 per share with warrants to buy 8.75m common at \$1.40). The placements may occur in two or more tranches. Investors will pay an up-front option fee to Bellicum of \$12.1m (\$0.125 for each common share underlying the preferred). Jefferies is the placement agent. (Aug.)

#### CLOVIS ONCOLOGY INC.

**Clovis Oncology Inc.** (solid tumor drug development) sold \$263m aggregate amount (net \$254.8m, including partial exercise of the over-allotment) of its 4.5% senior notes due 2024 in a private placement to institutional buyers. The notes convert to common at a rate of 137.2213 shares per \$1k principal amount, or about \$7.29 per share. (The company's stock averaged \$10.13 at the time of the sale.) Clovis will use the proceeds to repurchase outstanding 2.5% senior notes due 2021, and will put any remaining funds towards development, marketing, and collaboration expenses. (Aug.)

#### DECIPHERA PHARMACEUTICALS INC.

**Deciphera Pharmaceuticals Inc.** (developing kinase switch control inhibitors for cancer) netted \$376m through an upsized public offering of 10.8 million common shares at \$37. (The company originally filed to sell \$200m of its shares.) Approximately \$72m of the proceeds will support continued development of lead candidate ripretinib, including a Phase III trial for gastrointestinal stromal tumors and two Phase I trials in systemic mastocytosis and other solid tumors. Funds will also go towards development of additional pipeline candidates, and will support the company's transition from a development-stage company to a commercial-stage firm. (Aug.)

Investment Banks/Advisors: Guggenheim Partners LLC; JP Morgan Chase & Co.; Jefferies & Co. Inc.; Piper Jaffray & Co.; SunTrust Banks Inc.

#### DEL CATH SYSTEMS INC.

**Delcath Systems Inc.** (interventional oncology) netted \$8.6m through a private placement of 9,510 series E-1 convertible preferred shares priced at \$1k. Each preferred share converts into 16,667 common at \$0.06. Investors (which included Rosalind Advisors and Altium Capital) also

received warrants to purchase 9,510 common, exercisable at \$0.06 and good for five years from the date of an anticipated stock split. Roth Capital was the placement agent. The sale follows the issuance last month by the company of 20k series E preferred shares for net proceeds of \$18.35m. (Aug.)

Investment Banks/Advisors: Roth Capital Partners

#### DYNAVAX TECHNOLOGIES CORP.

**Dynavax Technologies Corp.** netted \$65.9m through a public offering of common and preferred shares. The company sold 18.5 million common shares at \$3 and issued 4,840 series B preferred shares (each convertible into 1k shares of common) at \$1k apiece. Investors also received a total of 5.8 million 30-month warrants to purchase common shares exercisable at \$4.50. Funds will support ongoing commercialization of *Heplisav-B* recombinant hepatitis B vaccine and will also go towards general corporate needs. (Aug.)

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

#### IRONWOOD PHARMACEUTICALS INC.

**Ironwood Pharmaceuticals Inc.** (developing treatments for gastrointestinal diseases including IBS) netted \$390m through an upsized private sale of \$400m aggregate amount (including the over-allotment) of its senior convertible notes. Institutional investors purchased \$200m aggregate principal amount of 0.75% notes due June 15, 2024, and \$200m aggregate principal amount of 1.50% notes due June 15, 2026. Both sets of notes convert to common at a rate of 74.6887 shares per \$1k principal amount, or approximately \$13.39 per share. (Ironwood's stock averaged \$10.40 at the time of the sale). Proceeds will allow the company to redeem all of its outstanding 8.375% notes due 2026; repurchase about \$215m aggregate principal amount of its outstanding 2.25% convertible notes due 2022; pay the cost of concurrent capped call transactions; and fund general corporate purposes. (Aug.)

#### MEIRAGTX HOLDINGS PLC

UK gene therapy start-up **MeiraGTX Holdings PLC** (specializes in viral vector design and optimization, manufacturing, and gene regulation technology) netted \$70.7m through the public sale of 3.2 million ordinary shares at \$23.50. The company will use the proceeds to fund ongoing development of its pipeline--which has six candidates in the clinic as well as preclinical and research programs--and expand its manufacturing capabilities, with plans to add a second viral vector facility outside the UK and a

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GMP plasmid production facility. (Aug.)  
 Investment Banks/Advisors: Bank of America Merrill Lynch; Chardan Capital Markets; Piper Jaffray & Co.

#### OBSEVA SA

Oxford Finance will provide **ObsEva SA** (women's reproductive health therapeutics) with a \$75m three-tranche senior secured credit facility, in which the company received \$25m upon closing. The loan bears a floating interest rate partially based on thirty-day US LIBOR rate (currently 8.68% per year) and will mature on August 1, 2024. (Aug.)

#### PORTOLA PHARMACEUTICALS INC.

**Portola Pharmaceuticals Inc.** netted \$212.6m through a public offering of 8 million common shares at \$28. The company develops therapies for blood disorders, and will use the offering proceeds to fund the launch of lead candidate *Andexxa* (coagulation factor Xa (recombinant), inactivated-zhzo) in the US (and in the EU, branded as *Ondexxya*) as a reversal agent for apixaban- or rivaroxaban-treated patients with uncontrolled bleeding. Money will also go towards post-marketing activities for the drug, and for general working capital. (Aug.)

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

#### SPRINGWORKS THERAPEUTICS INC.

**SpringWorks Therapeutics Inc.** (developing treatments for cancer and rare diseases) filed for its initial public offering. (Aug.)  
 Investment Banks/Advisors: Cowen & Co. LLC; Goldman Sachs & Co.; JP Morgan Chase & Co.; Wedbush PacGrow Life Sciences

#### STEMLINE THERAPEUTICS INC.

**Stemline Therapeutics Inc.** (oncology) netted \$71.7m through the public sale of 5 million common shares at \$15.25. Proceeds are earmarked for commercialization of *Elzonris* (tagraxofusp) for blastic plasmacytoid dendritic cell neoplasm; trials with that candidate in additional indications, including chronic myelomonocytic leukemia, myelofibrosis, acute myeloid leukemia, and potentially certain lymphomas; and for development and regulatory activities with other pipeline projects. (Aug.)

Investment Banks/Advisors: Aegis Capital Corp.; Alliance Global Partners; Cantor Fitzgerald & Co.; Cowen & Co. LLC; HC Wainwright & Co.; JP Morgan Chase & Co.; Ladenburg Thalmann & Co. Inc.; ThinkEquity Partners LLC

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