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Regenerative medicine becomes a reality

As a result of the recent landmark gene therapy and chimeric antigen receptor T cell approvals, momentum is building in the field of regenerative medicine. Increased funding and regulatory support has brought confidence to developers that are now bringing a new generation of concepts to the clinic.

Cormac Sheridan

The landmark Food and Drug Administration (FDA) approvals last year of the first chimeric antigen receptor T cell (CAR-T) therapies and the first US gene therapy represent the culmination of decades of research. They are also the harbingers of a new era of regenerative medicine, which has, after several false dawns, now started to unfold at a rapid pace **(Table 1)**. Much of the decades-long promise of biotechnology has been embodied in cell and gene therapies—and that promise is finally being realized, with the help of a massive mobilization of capital **(Table 2)**. The influx of cash is propelling these novel therapies and their underlying technologies through the necessary processes of industrialization and scaleup required to transform promising but risky development programs into high-quality, commercial products that can make a real difference to patients.

The present juncture represents an inflection point for the biotechnology industry—you could call it 'Biotechnology 3.0'—as cell and gene therapies start to take their place alongside the enzyme-replacement therapies and other protein-based drugs that emerged in the 1980s, and the antibody drugs that followed in the 1990s and succeeding decades. "You're seeing now the result of 5 to 10 years of building capacity and expertise. Now it's time to deliver," said Bastiano Sanna, CEO of Semma Therapeutics, of Cambridge, Massachusetts, which is developing encapsulated stem cell therapies for the treatment of diabetes.

What is regenerative medicine?

Regenerative medicine is a loose concept that covers a multitude of therapeutic approaches and technologies. In broad terms, it refers to therapies intended to regrow, repair or replace diseased or damaged cells, tissues or organs. The Alliance for Regenerative Medicine (ARM) defines the space by therapeutic modality rather than therapeutic intent: its practical interpretation of the term includes cell and gene therapies and tissue engineering—all of which share commonalities in terms of manufacturing and regulation. Within the burgeoning field of immuno-oncology, for example, CAR-T therapies and genetically engineered oncolytic viruses are classed as regenerative medicines, but antibody-based immune checkpoint inhibitors are not. The global pipeline of therapies now in development across the wider regenerative medicines space is large: at the end of the first quarter (Q1) of 2018, a total of 959 clinical trials were underway, including 319 involving gene therapy, 284 involving gene-modified cell therapy, 332 involving cell therapy and 24 involving tissue engineering.

It takes significant levels of capital to fuel all of this effort. According to ARM's data, companies in the regenerative medicines space raised $3.8 billion in investment from the public and private capital markets and from upfront payments in licensing deals during Q1 2018. This total is up 135% from the same period in 2017. Early-stage companies are routinely raising upwards of $100 million in series A deals. Privately held companies now have a level of financial muscle and capability that would have been unthinkable even in the recent past. The leaders of CAR-T pioneer company Kite Pharma—sold last year to Gilead Sciences for $11.9 billion—have regrouped at new start-up Allogene Therapeutics, which raised $300 million to develop a portfolio of allogeneic (off-the-shelf) CAR-T therapies. Pfizer originally licensed these assets from genome-editing firm Cellectis, but entered an alliance with Allogene in order to tap into Allogene's expertise. Celgene, in addition to acquiring another major CAR-T player Juno Therapeutics, for $9 billion, has spun out its regenerative medicine division into another new firm, Celularity, to accelerate the development of a broad pipeline of clinical and preclinical programs in cell therapy, immuno-oncology and 'functional regeneration'. Celularity raised $250 million in initial funding, and Celgene retains options on a number of its programs.

Celularity is just one of a small handful of companies that is bringing a new cell type into regenerative medicine. CEO Bob Hariri, a serial biotech entrepreneur, has honed in on the placenta as a rich source of allogeneic cells and stem cells with distinct biological and immunological profiles, arising from its role in supporting and controlling the development of the fetus. "It is a bioreactor; it is a cell expansion and cultivation environment," said Hariri. "It comes with a beautiful coaxial cable attached," he added, referring to the umbilical cord, which underpins Celularity's existing cord blood banking services. Celularity has forged partnerships with Sorrento Therapeutics, to gain access to the latter's antibody engineering and CAR-T technologies, and with Human Longevity, Inc.—which Hariri cofounded—to build genomics profiles of the living donors who provide Celularity with placental tissue. Its lead immuno-oncology therapy PNK-007, which comprises expanded unmodified placental natural killer cells, is undergoing a phase 1 trial in patients with multiple myeloma who have undergone autologous bone marrow transplant. Celularity has completed a phase 2 trial of a mesenchymal stem cell therapy in Crohn's disease, and phase 2 trials of mesenchymal stem cell therapies in patients with diabetic foot ulcer or diabetic peripheral neuropathy are ongoing.

Uptick in mergers and acquisitions activity

Mergers and acquisitions activity during Q1 2018 was also well ahead of that of the previous year—the $9.1 billion total reached during the quarter was 70% of the $13.5 billion total reached during

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Table 1 | Selected cell and gene therapies on the market and in development

Developer	Product	Description	Indication	Development status
Novartis and the University of Pennsylvania	Kymriah (tisagenlecleucel)	CD19-directed autologous CAR-T therapy	B cell acute lymphoblastic leukemia and large B cell lymphoma	FDA approved, EU approval pending
Kite Pharma and Gilead Sciences	Yescarta (axicabtagene ciloleucel)	CD19-directed autologous CAR-T therapy	Large B-cell lymphoma	FDA approved, EU approval pending
Spark Therapeutics	Luxturna (voretigene neparvovec-rzyl)	AAV2-based gene therapy encoding RPE65	Biallelic RPE65 mutation-associated retinal dystrophy	FDA approved
TiGenix and Takeda	Alofisel (darvadstrocel; Cx601)	Allogeneic adipose-derived mesenchymal stem cell therapy	Crohn's disease	EU approved
Orchard Therapeutics Ltd., GlaxoSmithKline and the San Raffaele Telethon Gene Therapy Institute	Strimvelis	Ex vivo stem cell therapy comprising autologous $CD34^+$ cells transduced with gammaretroviral vector (based on Moloney murine leukemia virus) expressing ADA	Severe combined immunodeficiency due to ADA deficiency	EU approved
Enzyvant	RVT-802	Allogeneic thymic tissue-based therapy for children born without a thymus	Complete DiGeorge anomaly	Rolling BLA initiated
Bluebird Bio	LentiGlobin	Ex vivo gene therapy comprising autologous $CD34^+$ cells transfused with lentiviral vector encoding engineered hemoglobin	Transfusion-dependent β-thalassemia	EU filing planned for 2018
Nightstar Therapeutics	NSR-REP1	AAV2 vector encoding REP1	Choroideremia	Phase 3
uniQure	AMT-061	AAV5 vector encoding the Padua variant of factor IX	Hemophilia B	Phase 3
AveXis and Novartis	AVXS-101	AAV9-based gene therapy encoding SMN1	Spinal muscular atrophy	Pivotal phase 2/3 trial

AAV, adeno-associated virus; ADA, adenosine deaminase; BLA, biologics license application; CAR-T, chimeric antigen receptor T cell; REP1, Rab escort protein 1; SMN1, survival motor neuron 1.

all of 2017. "This past year has been really a watershed year for the sector," said ARM CEO Janet Lambert. "The clinical news and scientific progress were evident. I think the arrival of the products on the US market was a breakout moment." The addition of one single transaction completed during Q2 2018—the $8.7 billion takeover of gene therapy developer AveXis by Novartis—pushes this year's running total well past last year's final tally. Data from a phase 1 trial of AveXis's lead therapy AVXS-101 in spinal muscular atrophy demonstrated a remarkable 100% survival benefit in patients with severe disease and grabbed the attention of the big pharma company. It was not the only company in the frame. "There was substantial interest. There were a number of companies following AveXis, with the clinical dataset we had," said Brian Kaspar, founder and CSO. Significantly, AveXis will continue to operate as an independent gene therapy subsidiary of Novartis, and will seek to replicate its present success in other diseases.

The significance of therapies such as AVXS-101 and the first wave of CAR-T therapies lies in their unprecedented clinical efficacy and their commercial potential, not necessarily in their being the first in their respective categories to gain approval. Europe approved its first gene therapy Glybera (alipogene tiparvovec) for lipoprotein lipase deficiency in 2012, and its second Strimvelis for severe combined immunodeficiency due to adenosine deaminase deficiency in 2016. A handful of cell therapies have also been approved in Europe dating back to 2009, when the cartilage repair therapy ChondroCelect became the first in its class to gain approval under the European Medicines Agency's Advanced Therapy Medicinal Product pathway. In the United States, Provenge (sipuleucel-T), a cell-based immunotherapy for prostate cancer, generated waves of hype in advance of its FDA approval in 2010 but never made much commercial headway thereafter. Most of these therapies offered marginal clinical benefit or very limited commercial opportunity—or both. Glybera and ChondroCelect have been withdrawn from the market, demonstrating that being the first mover may not be an advantage—and does not automatically lead to commercial sustainability.

Having decided to exit the rare disease space, GlaxoSmithKline recently handed on commercial rights to Strimvelis to Orchard Therapeutics Ltd., a gene therapy startup, in return for equity. The developer of ChondroCelect, TiGenix, successfully absorbed the lessons from that experience and achieved another first, by gaining European Medicines Agency approval for an allogeneic stem cell therapy, Alofisel (darvadstrocel), which is licensed to treat complex perianal fistulas in adult patients with Crohn's disease. Reaching that milestone prompted a $630 million buyout offer from its development partner Takeda, of Osaka, Japan, earlier this year. "It's still early days. I think the European experience has been helpful in the US market, and hopefully the reverse will be true," said Lambert.

Technological transitions

The present era of gene therapy and cell therapy has been enabled by scientific and clinical progress on multiple fronts. It is now undergoing a transition from grappling with complex biological questions to what Ken Mills, CEO of gene therapy firm Regenxbio, calls "linear engineering problems". Companies have learned how to deliver gene therapy vectors to different tissues, including the liver, retina, muscle and central nervous system, for example. They have also become more comfortable with delivering high doses of vector without imposing dangerous levels of toxicity on patients. "That has brought up another question about manufacturing," he said. "It's shifted the conversation from 'can you put enough in?' to 'can you make enough?'" Some critics have warned that current process technologies are not equipped to deal with a large-scale rollout of gene therapy, particularly in cases in which high systemic doses are required, to large patient populations. Regenxbio's CSO Olivier Danos disagrees. "I'm pretty sure we'll have a fivefold to tenfold improvement in the next few years," he said. "I'm sure we've not reached the limit of what can be done."

Regenxbio began life as a platform company offering access to its adeno-associated virus (AAV) vector technology, based on

Table 2 | Recent investments in regenerative medicine companies

Company	Technology	Transaction	Date	Amount raised ($ millions)
Neon Therapeutics	Peptide vaccines and ex vivo cell therapies targeting cancer neoantigens	IPO	June 2018	100
Autolus Therapeutics	CAR-T therapy	IPO	June 2018	150
Avrobio	Ex vivo lentiviral-based gene therapy for rare diseases	IPO	June 2018	99
Decibel Therapeutics	Gene therapy for hearing loss	Series C financing	June 2018	55
Freeline Therapeutics	Gene therapy for hemophilia	Series B financing	June 2018	115
SwanBio Therapeutics Ltd.	Gene therapy for inherited central nervous system disease	Series A financing	June 2018	23
Humacyte	Humacyl (synthetic blood vessels based on human connective tissue and proteins)	19% stake acquired by Fresenius Medical Care	June 2018	150
MeiraGTx Holdings	Gene therapy for ophthalmology, salivary gland and neurodegenerative conditions	IPO	June 2018	75
Uniqure	Gene therapy	Secondary share offering	May 2018	147
Sangamo Therapeutics	Genome editing with zinc finger nucleases	Secondary share offering	April 2018	230
Unum Therapeutics	Autologous T cell therapy engineered to express antibody-coupled T cell receptor	IPO	March 2018	69
Homology Medicines	Gene therapy employing AAV vectors isolated from human $CD34^+$ hematopoietic stem cells, which have a liver tropism	IPO	March 2018	144
Humacyte	Humacyl (synthetic blood vessels based on human connective tissue and proteins)	Series C financing	March 2018	75
Rubius Therapeutics	Allogeneic cell therapy based on enucleated red blood cell protein factories	Crossover financing	March 2018	100
Celularity	Cell therapies derived from allogeneic placental platform	Series A financing	February 2018	250
Audentes Therapeutics	Gene therapy for rare diseases	Secondary share offering	January 2018	231
Solid Biosciences	AAV9-based gene therapy for Duchenne muscular dystrophy	IPO	January 2018	125
AveXis	Gene therapy for neurological genetic diseases	Secondary share offering	January 2018	431
Bluebird Bio	Gene therapy for inherited neurodegenerative and hematological disease and cancer	Secondary share offering	January 2018	651

CAR-T, chimeric antigen receptor T cell; IPO, initial public offering.

the research of James Wilson at the University of Pennsylvania, Philadelphia. It has since employed its own technology in several inhouse development programs in retinal, metabolic and neurodegenerative disease. It also remains, Danos said, "in the eye of the hurricane" because of its relationships with multiple companies, including Biogen, Ultragenyx, Shire, Audentes Therapeutics, Voyager Therapeutics, Prevail Therapeutics, Esteve and AveXis. Some 20 gene therapy development programs employ Regenxbio's AAV technology, including AVXS-101, the AveXis-developed AAV9-based gene therapy for spinal muscular atrophy that triggered the Novartis deal. Regenxbio was a secondary beneficiary, pocketing $100 million under its agreement with Avexis, with up to $80 million more plus sales royalties to come. "The fact that Novartis has made an investment in AveXis at this level is a very important validation of the technology," Danos said.

There is plenty of scope to improve the technologies that underpin gene therapy, however. For example, immunogenicity, arising from either the capsid or therapeutic proteins, remains a significant problem. Systemic immunosuppression, which is routinely deployed for life-threatening conditions, is not a viable option for many other diseases. "It's pretty clear we still need to do better there," Danos said. "I don't think this is sustainable." Precise induction of immune tolerance to specific proteins is being explored but has yet to reach the clinic, he noted. Better control of the introduced construct through molecular switches is also an important topic—the ability to turn the production of a protein up or down—or off and on—could extend gene therapy to conditions where it is currently not feasible. "Today we can't do that," he said.

Becoming a reality

Gene and cell therapy have followed a similar development trajectory to that of earlier technologies, which are now deeply embedded in the biotech industry and in clinical practice. The hype that accompanied their initial emergence then gave way to disillusion when initial results failed to match expectations. "The press and the investor community have become frenetic in demanding perfection from the get go," said Sanna. But drug development and the wider development of medical knowledge are iterative, gradual processes. "There is no reason why cell therapy should be any different," he said. The field has now entered a more realistic stage in its development—real progress has been achieved in some areas, such as oncology, rare diseases, hematologic diseases and inherited retinal conditions. Success in other areas, particularly complex conditions, such as cardiovascular disease and neurodegenerative conditions, such as Parkinson disease, is still elusive, notwithstanding significant ongoing research investments. "The heart is such a mechanically complex organ," said Sanna.

But the field has reached a point where, as Kaspar notes, it has greater confidence about the tools at its disposal and a better understanding of the nuances of delivering therapies to specific locations. The accumulated knowledge will help developers move from monogenic conditions into complex diseases. "It's going to require the next round of substantial investment," he said. On current evidence, that money is already there.

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