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Next-generation therapeutics: cell and gene therapy gathers pace

At one of its most exciting phases of growth, the cell and gene therapy market has gained momentum in dealmaking, product sales and big pharma interest, all of which are analyzed in this feature.

Paul Verdin and Lisa Urquhart

Therapeutic approaches employing whole cells are not new—for example, techniques based on cultured autologous epidermal cells for burn treatment and chondrocytes for knee cartilage repair have been available for more than a decade. Gene therapy and other gene transcription and translation-targeted approaches such as RNA interference (RNAi) are a much more recent addition to the therapeutic arsenal, and coupled with the high-profile arrival of chimeric antigen receptor (CAR)-T cells are ushering in a new era for cell-based and gene-based medicine.

These groundbreaking scientific advances have also brought with them intense debate about payment models and affordability, adding fuel to the broader fire raging around drug pricing. Nonetheless, sell-side consensus forecasts from Evaluate Pharma project growth of the combined cell, gene and nucleic acid therapy market from $1 billion in 2017 to $44 billion in 2024, resulting in a staggering 65% compound annual growth rate **(Fig. 1)**. With such value at stake, this has been—and will likely continue to be—one of the most keenly watched pharma segments for business development groups and industry observers alike in the next few years.

Cell-based and gene-based medicine comes of age

In 2017, the first products harnessing CAR-T cells to treat cancer were approved by the US Food and Drug Administration (FDA)—Novartis's Kymriah (tisagenlecleucel) for acute lymphoblastic leukemia and Kite Pharma's (now Gilead Sciences') Yescarta (axicabtagene ciloleucel) for non-Hodgkin's lymphoma (NHL). Shortly after in the same year, Spark Therapeutics' Luxturna (voretigene neparvovec) became the first FDA-approved in vivo gene therapy, for inherited retinal dystrophy. Then in 2018, the FDA approval of Alnylam Pharmaceuticals' Onpattro (patisiran), a pioneering RNAi therapy for polyneuropathy caused by hereditary transthyretin-mediated amyloidosis, rounded off a remarkable string of 'firsts' for cell-based and gene-based medicine. There have also been notable approvals of oligonucleotide-based therapies with antisense and exon-skipping mechanisms in the past few years, including Ionis Pharmaceuticals' Tegsedi (inotersen), also for polyneuropathy caused by hereditary transthyretin-mediated amyloidosis, Biogen's Spinraza (nusinersen) for spinal muscular atrophy (SMA) and Sarepta Therapeutics' Exondys 51 (eteplirsen) for Duchenne muscular dystrophy (DMD). Whereas the CAR-T approach is somewhat different, and focused on oncology, the other approvals represent major advances in the broader field of 'regenerative medicine,' offering the prospect of major advances and perhaps even cures for previously intractable diseases.

However, these recent catalysts might only be the tip of the iceberg. Evaluate's analysis reveals >5,000 active research and development programs for cell-based and gene-based medicine, and while there is substantial ongoing work in oncology, the majority of programs (65%) across the combined pipeline are in non-oncology indications. The value picture reveals a similar overall distribution—indications outside oncology account for 76% of the 2024 forecasted sales value, and only three oncology indications are included in the top 20 indications by 2024 forecast sales **(Fig. 2)**. The top 20 list reveals a wide variety of indications, including SMA, amyloidosis, hemophilia A and B, sickle cell disease, Huntington's disease and amyotrophic lateral sclerosis. Logically, nucleic acid approaches are on the whole focused on those diseases with a clearer genetic basis, whereas cell therapies are being explored in oncology and those indications with a more complex etiology. The indications attracting the biggest sales forecasts include those for which drugs have already been approved (including DMD, NHL and SMA), helping to derisk forecasts.

Participants in the cell and gene therapy field

In terms of the companies involved in the cell and gene therapy space, thus far, major pharma has largely stayed on the periphery—only five companies that are considered established large pharma players are included in the top 20 by 2024 sales: Novartis, Gilead, Biogen, Celgene and Takeda **(Fig. 3)**. The top ranked company by forecasted 2024 sales is Sarepta, driven in part by the marketed Exondys 51 for DMD, but primarily through growth from a variety of nucleic-acid-based pipeline programs including further exon-skipping antisense and gene therapy programs in muscular dystrophy. Overall, Sarepta's pipeline is forecasted to generate >$3 billion in 2024 sales.

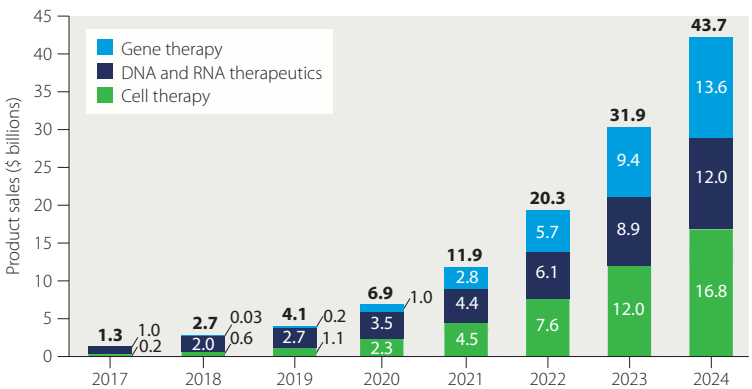

Fig. 1 | Sales growth trends of cell, gene and nucleic acid therapy products from 2017 to 2024. Source: EvaluatePharma, March 2019.

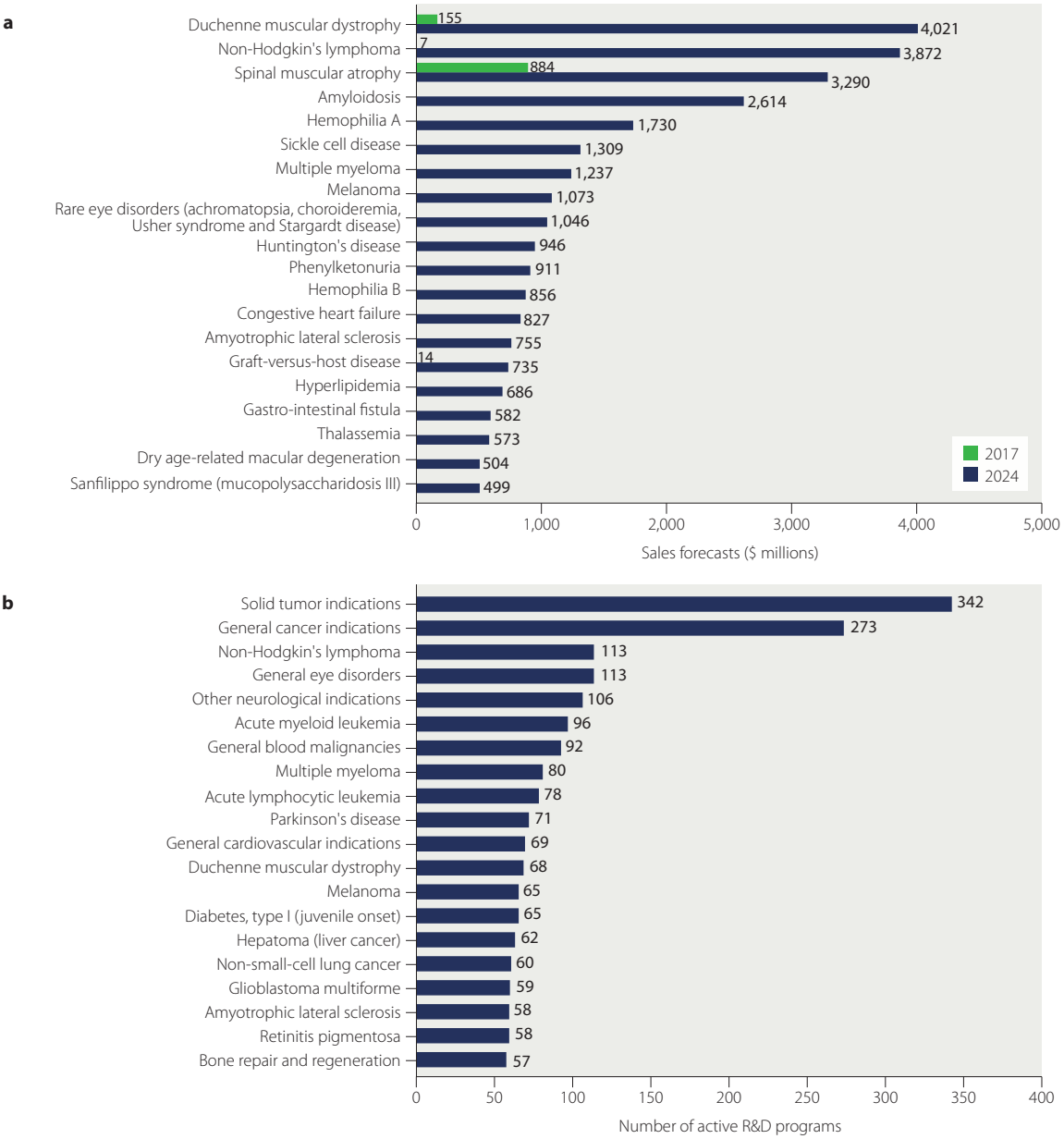

Fig. 2 | Top 20 indications in the field of cell, gene and nucleic acid therapies, based on 2024 sales forecasts and number of active R&D programs. R&D, research and development. Source: EvaluatePharma, March 2019.

The top 20 list is populated by other smaller players that have rapidly become well-watched names on the basis of their focus on cell-based and gene-based medicine, including bluebird bio, Alnylam, BioMarin Pharmaceutical and Spark—the announced acquisition of the latter by Roche in February, expected to close in Q2 2019, is proof that this area will continue to be closely watched by big pharma.

Leading dealmakers

Other standout deals by major players in recent years include a number of acquisitions and strategic collaborations that have already yielded results (**Table 1**). Novartis's 2018 acquisition of AveXis is the biggest deal in gene therapy at $8.7 billion (an 88% share price premium), enabling the big pharma company access to technology and a pipeline of assets in life-threatening neurological diseases, including SMA. In cell therapy, the acquisitions of Kite and Juno by Gilead ($11.9 billion) and Celgene ($9 billion), respectively, gave the larger groups access to CAR-T platforms and advanced pipeline candidates. For Gilead, this has already delivered a marketed product in Yescarta.

Outside oncology, Takeda announced in 2018 its intent to acquire TiGenix for $626 million, providing access to a platform based on allogeneic expanded adipose-derived stem cells targeted at gastroenterology conditions—a deal that has delivered the larger group a marketed asset in Alofisel (darvadstrocel). The nucleic-acid-based therapeutics landscape has been less of a target for standout acquisitions, but Biogen's expanded tie up with Ionis is notable. Under the terms of the expanded 2018 deal, Biogen will pay Ionis a total of $1 billion upfront for a ten-year collaboration focused on developing antisense products for a range of neurological diseases. The collaboration builds on a relationship that successfully delivered Spinraza to the market. And in April 2019, Regeneron Pharmaceuticals' announcement that it would invest $800 million in Alnylam to collaborate on RNAi therapies across multiple disease areas underlined the interest in this platform following the first RNAi approval in 2018.

Clearly many major players—as well as industry observers—have their eyes on cell-based and gene-based medicine as a new era in disease management and, potentially, cure. There is justifiable cause for excitement with the range and profile of regulatory successes in recent years. However, owing to the well-documented but unsolved commercial challenges for such products once on the market, reasonable valuations are very difficult to measure. The

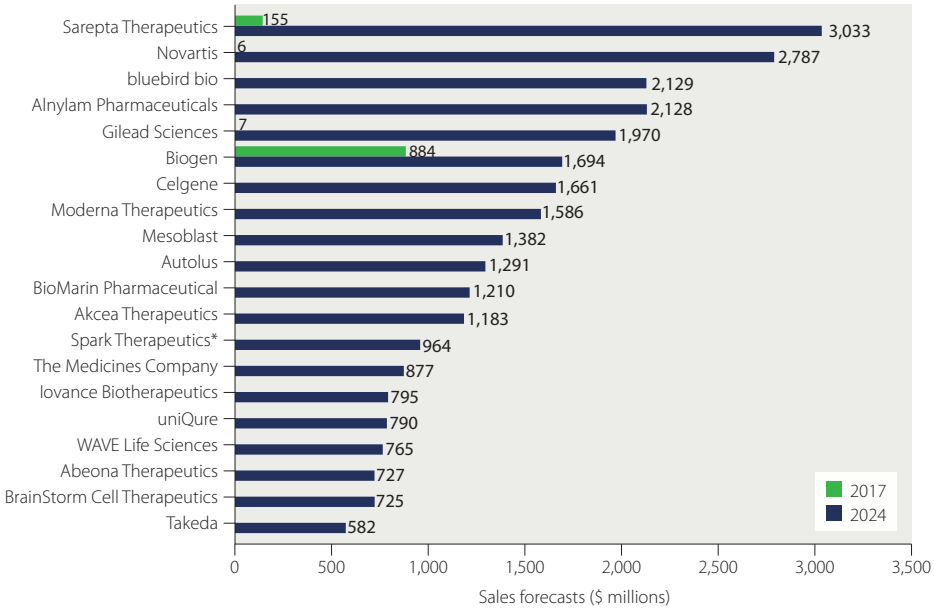

Fig. 3 | Top 20 companies in the field of cell, gene and nucleic acid therapies, based on 2024 sales forecasts. *Acquisition by Roche announced in February 2019. Source: EvaluatePharma, March 2019.

numerous smaller players leading the way could try to go it alone to market (many already have), and the focused eligible patient populations involved could reduce the barriers to such an endeavour. Otherwise it might be reasonable to expect more deals in this space. Whatever the case, the clinical and commercial impact of the recently introduced cell-based and gene-based therapies will be fascinating to watch and will no doubt continue to generate headlines—and the sell-side view of $44 billion sales in 2024 will be put to the test.

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Table 1 | Selected recent deals related to cell, gene and nucleic acid therapies

Deal date	Companies	Deal type	Platform	Deal summary
April 2019	Regeneron Pharmaceuticals and Alnylam Pharmaceuticals	In-licensing	RNAi	Regeneron Pharmaceuticals partners with Alnylam Pharmaceuticals in a deal to develop and commercialize RNAi therapeutics for eye and neurological disorders, which could be worth up to $1 billion, including $800 million upfront (cash plus equity) from Regeneron
February 2019	Roche and Spark Therapeutics	Acquisition	Gene therapy	Roche announces the acquisition of Spark Therapeutics for a total equity value of $4.8 billion, with Spark Therapeutics continuing operations as an independent company within the Roche Group
October 2018	Johnson & Johnson and Arrowhead Pharmaceuticals	In-licensing	RNAi	Janssen obtains a worldwide license for Arrowhead Pharmaceuticals' ARO-HBV and an option to collaborate on up to three new RNAi candidates for $250 million upfront (cash plus equity) with a total deal value of up to £3.7 billion
September 2018	Amicus Therapeutics and Celenex	Acquisition	Gene therapy	Amicus Therapeutics acquires Celenex, a gene therapy company spin-out of Nationwide Children's Hospital, for $452 million ($100 million upfront plus contingent components)
August 2018	PTC Therapeutics and Agilis Biotherapeutics	Acquisition	Gene therapy	PTC Therapeutics acquires Agilis Biotherapeutics, accessing an innovative gene therapy platform for rare monogenic central nervous system diseases, for $945 million
July 2018	Takeda and TiGenix	Acquisition	Cell therapy	Takeda acquires TiGenix, accessing novel technology based on the anti-inflammatory properties of allogeneic stem cells, for $626 million
May 2018	Novartis and AveXis	Acquisition	Gene therapy	Novartis acquires AveXis to advance its pipeline of gene therapies in life-threatening neurological genetic diseases for $8.7 billion
April 2018	Biogen and Ionis Pharmaceuticals	In-licensing	Antisense and exon-skipping	Biogen and Ionis Pharmaceuticals expand the collaboration that delivered Spinraza (nusinersen) with a new ten-year term to develop novel antisense drug candidates for a broad range of neurological diseases including dementia, neuromuscular diseases, movement disorders, ophthalmology, diseases of the inner ear and neuropsychiatry; Biogen to pay a total of $1 billion upfront
January 2018	Celgene and Juno Therapeutics	Acquisition	Cell therapy	Celgene acquires Juno Therapeutics, accessing its CAR-T portfolio for $9 billion
October 2017	Gilead and Kite Pharma	Acquisition	Cell therapy	Gilead acquires Kite Pharma, accessing its CAR-T portfolio for $11.9 billion
August 2016	Pfizer and Bamboo Therapeutics	Acquisition	Gene therapy	Pfizer acquires Bamboo Therapeutics and access to gene therapy candidates for rare neuromuscular and central nervous system diseases for $645 million
April 2016	Regeneron Pharmaceuticals and Intellia Therapeutics	In-licensing	Gene therapy	Regeneron Pharmaceuticals acquires exclusive worldwide rights to advance CRISPR–Cas gene-editing technology for therapeutic development; over a six-year period Regeneron Pharmaceuticals has rights to develop CRISPR-based products against up to ten liver targets for $75 million upfront and a total potential deal value of >$3 billion

CAR-T, chimeric antigen receptor-T cell; RNAi, RNA interference. Source: EvaluatePharma, March 2019.