In 2019, the regenerative medicine sector saw significant growth. Thousands of patients are now benefiting from commercial regenerative medicines, and the impact of early cell and gene therapies is dramatic. The clinical pipeline is robust, with nearly a hundred Phase 3 trials underway, several late-stage products poised for approval, and next-generation technologies such as gene editing beginning to enter the clinic. Therapeutic developers are increasing their focus on solving manufacturing challenges. The sector continued to attract billions in investment, further fueling our scientific, clinical, and commercial progress.
and patient advocates – are incredibly knowledgeable and motivated to bring these therapies to patients across the globe, and we at ARM are grateful to be spearheading efforts to get safe and effective medicines to patients.

Since I came to ARM in 2017, this sector has really come of age – and there is still so much more to come. While 2019 was very successful, we still have considerable work to be do together to ensure that the early clinical promise and commercial successes of these therapies translates to widespread patient access. With that in mind, I wanted to share some of the major trends we’ve seen in 2019, as well as the outlook for 2020.

GLOBAL FINANCINGS

Regenerative medicine sector financings trended positively in 2019 compared to five- and ten-year data, with this past year finishing as the second-strongest year on record. Investment activity, corporate partnerships, and mergers and acquisitions flourished as the nearly 1,000 therapeutic developers active in this space worked to bring their products to patients worldwide. These 987 developers tracked by ARM raised $9.8B, including $7.6B in gene therapy, $5.1B in cell therapy, and $442M in tissue engineering [Footnote 1].

In particular, 2019 was a strong year for venture capital activity in the cell and gene therapy space, with developers raising $4.1B in venture financing – a 32% increase year-over-year from 2018. Notable venture financings from 2019 include Century Therapeutics’ launch with $250M to develop iPSC-based allogeneic cell therapies; Maze Therapeutics $191M debut; and Poseida Therapeutics’ $142M Series C financing.

In addition, corporate partnerships in the cell and gene therapy space totaled to $1.5B in upfront value, with potential royalties and milestone payments worth up to $17.6B [Footnote 2]. Many of these partnerships focused on developing therapies for non-monogenetic disorders, reflecting increased clinical development in indications with larger patient populations. These partnerships included a $150M upfront partnership between Grunenthal and Mesoblast to develop Mesoblast’s cell therapy for lower back pain; REGENXBIO and

“These 987 developers... raised $9.8B, including $7.6B in gene therapy, $5.1B in cell therapy, and $442M in tissue engineering.”

1. Financings by companies active in gene-modified cell therapies are counted in both the gene therapy and cell therapy categories; as such, these categories do not add up to the total financings figure. The total financings figure does not include M&A, which is calculated separately.

2. Only upfront payments are included in the total financings figure.
Neurimmune’s collaboration to develop gene therapies for tauopathies; Verve Therapeutics and Beam Therapeutics’ agreement to develop gene-edited therapies for cardiovascular disease; and AbbVie and Voyager’s $65M agreement to develop gene therapies for Parkinson’s disease.

There continued to be significant M&A activity in the sector, as large- and mid-cap pharma look to expand their regenerative medicine portfolios by acquiring smaller developers. Upfront payments for mergers and acquisitions in 2019 totaled $11.3B – not including Astellas Pharma’s $3B acquisition of neuromuscular gene therapy developer Audentes, which closed early in Q1 2020. Other notable acquisitions this year include Roche’s $4.3B acquisition of Spark Therapeutics, Vertex’s $850M acquisition of Sema4 Therapeutics, Biogen’s $877M acquisition of Nightstar Therapeutics, and Bayer’s $240M payment to acquire the remaining stake in BlueRock Therapeutics.

**PATIENT IMPACT**

Already, regenerative medicine products are providing a significant positive clinical benefit to patients with severe diseases and disorders, many of whom previously had few or no treatment options available. In the USA, we estimate that approximately 4,500 to 5,500 patients have already been treated with FDA-approved gene therapies and gene-modified cell therapies, and thousands of additional patients treated with early generation cell and tissue products.

In oncology, CAR-T therapies Yescarta and Kymriah are providing 40 to 80% complete response rates for patients suffering from what would have once been terminal hematological malignancies. Novartis’s gene therapy Zolgensma is durably treating spinal muscular atrophy (SMA), including SMA Type 1, a serious genetic disorder that, in the past, was nearly always fatal by age 2. bluebird bio’s Zynteglo promises an alternative to patients with severe beta thalassemia, who have historically relied on regular transfusions – which often had long-term impacts on their overall health – to control their disease. And Luxturna has drastically improved the vision of patients with a rare inherited blindness-causing retinal disease.

The number of patients expected to benefit from regenerative medicines will only increase. Globally, regenerative medicine clinical trials have a combined target enrollment of over 60,000 patients, suffering from a diverse array of rare and prevalent indications. MIT NEWDGIG predicts that by 2030, over 500,000 patients will have been treated with a cell or gene therapy in the USA alone [2]. In 2019, developers filed for marketing authorizations for 10+ regenerative medicines, many of which we expect to be approved in 2020. These include the first gene therapies for hemophilia A (BioMarin) and metachromatic...
leukodystrophy (Orchard Therapeutics), two additional CAR-T products (Bristol Myers Squibb’s liso-cel and Kite/ Gilead’s KTE-X19), Mesoblast’s cell therapy for graft-versus-disease as well as their cell therapy, co-licensed with JCR Pharmaceuticals, for epidermolysis bullosa, and Enzyvant’s tissue-engineered product for pediatric congenital athymia. Officials from the US FDA [3] and European Medicines Agency (EMA) [4] have said that by 2025, they expect to be approving 10–20 cell and gene therapy products each year.

**CLINICAL & SCIENTIFIC ADVANCES**

2019 was a particularly significant year for the sector with immense scientific and clinical progress, particularly in gene-modified cell therapies and in gene editing products. Therapeutic developers are increasingly turning to indications with large patient populations, including cardiovascular disorders, diabetes, and age-related neurodegenerative diseases.

The regenerative medicine clinical pipeline is robust, looking to provide a durable or even curative therapeutic benefit for patients in more than 500 indications. As of the end of 2019, there were 1,066 ongoing clinical trials in regenerative medicine, including 94 in Phase 3, and the clinical landscape is continuing to expand.

In particular, gene-modified cell therapies are entering the clinic in record numbers, making up more than half of Phase 1 trials. On a panel on Emerging Cell Therapies at ARM’s State of the Industry Event, CRISPR Therapeutics CEO Samarth Kulkarni said that, “Cell therapies are here to stay in cancer,” predicting that cell therapies would make up at least one third of the market for therapies for liquid tumors within the next 5–6 years.

Allogeneic cell-based immunotherapies in particular are reaching clinical viability as developers improve strategies to deal with immunogenicity. In April 2019, Fate Therapeutics announced that they had dosed the first patient with their FT500 allogeneic NK cell therapy and Precision BioSciences announced that they had dosed the first patient in their allogeneic CAR-T clinical trial. Many researchers are continuing to explore iPSCs and gene editing technologies as strategies to deal with immunogenicity and allow for the development of additional ‘off-the-shelf’ therapies.

When Claudia Mitchell, Senior Vice President of Product & Portfolio Strategy at Astellas Pharma, was asked during the Emerging Cell Therapies panel if she thought allogeneic therapies would replace autologous therapies, she replied: “Absolutely.” Therapeutic developers are also looking to expand the application of CAR-Ts and other adoptive cell therapies outside of oncology. In 2019, Cartesian initiated the first CAR-T clinical
trial for an autoimmune disorder (generalized myasthenia gravis), and Sangamo Therapeutics received UK authorization to begin a clinical trial of their CAR-Treg product TX200 to prevent immune rejection following kidney transplantation.

Traditional gene therapies also make up a large percentage of the regenerative medicine clinical pipeline, with approximately one third of ongoing trials utilizing this technology. Researchers drove progress in gene therapy delivery in 2019, with many of these advances focused on improving efficiency of gene delivery methods, as well as on driving vector manufacturing processes. Non-viral gene therapy delivery also continues to advance. There are currently 57 ongoing gene therapy clinical trials utilizing non-viral delivery methods, and the first non-viral gene therapy, Colletagene, was approved in Japan to treat critical limb ischemia this past spring. Though it makes up a much smaller proportion of the clinical pipeline, genome editing had a watershed year in 2019. There are currently 31 early stage clinical trials ongoing worldwide utilizing genome editing, including trials in oncology (20 trials), inherited disorders (8 trials), and HIV (3 trials). CRISPR joined ZFNs and TALENs in the clinic this year, with early signs of positive clinical benefit reported by Tmunity / Penn Medicine for their CRISPR-edited CAR-T for patients with multiple myeloma and sarcomas, and by Vertex /CRISPR Therapeutics for their gene-edited product for beta thalassemia and sickle cell disease. In addition, Sangamo reported evidence of successful in vivo editing in their Phase 1/2 trial utilizing ZFNs. Looking forward, Editas plans to treat the first in vivo CRISPR patient in a clinical trial this year.

As this technology advances, it continues to be the focus of international dialogue on bioethics. While genome editing has proven itself to be a powerful tool in the search for cures for many serious diseases, germline editing, which makes heritable changes in the human genome – in contrast to somatic cell editing, in which the effects are limited to the patient treated – continues to present important safety, ethical, legal, and societal issues. In August 2019, 15 leading therapeutic developers active in gene editing signed on to ARM’s Statement of Principles, asserting that germline modifications are currently inappropriate for in-human use, and the World Health Organization launched an advisory committee to implement international mechanisms for oversight of clinical gene editing.

There is also an increased focus on clinical development for regenerative medicines for indications with larger patient populations. In the panel on Next Generation Cell & Gene Technologies, Senti Bio CEO Tim Lu said, “We need to try to figure out how to enable greater access to cell and gene therapies into other indications [...] how do we go beyond making single changes, single modifications, which I think are inherently limited to certain types of diseases [...] I think it’s pretty clear now from the basic research side that it’s possible. The design cycle for modifying and making these sort of therapies is only going to accelerate over the next decade and it’s a matter of how do we then take that pattern, match that with the right indications, and really drive those into the clinic.”

While much of the clinical development landscape is dominated by oncology and rare monogenetic disorders, an increasing number of clinical trials are ongoing in more common indications. These include...
common cardiovascular indications, such as myocardial infarction, peripheral artery disease, and critical limb ischemia (40 ongoing trials); diabetes and related complications (23 ongoing trials); aging-associated neurological disorders such as Parkinson’s, Alzheimer’s, and macular degeneration (19 ongoing trials); common musculoskeletal injuries and disorders (15 ongoing trials); and stroke and stroke recovery (10 ongoing trials). It is likely that these indication areas in particular will drive increased uptake of regenerative medicines going forward.

MANUFACTURING

As the number of patients receiving regenerative medicines increases, both through clinical trials and approved products that have come to market, companies across the clinical development timeline are implementing strategies to deal with manufacturing, CMC requirements, and scale up. This is particularly true as expedited approval programs, such as FDA’s RMAT designation, EMA’s PRIME designation, and Japan’s SAKIGAKE designation, provide pathways for earlier approval, shortening development timelines. In 2019, 17 regenerative medicine products received one or more of these designations. Looking to meet the growing supply needs for cell and gene therapies, many larger companies made headlines in 2019 with plans for expansive facilities to improve their in-house manufacturing capabilities. In particular, Pfizer and Novartis have shared plans to invest a combined $2 billion on gene therapy production. For larger companies, CMOs are attractive acquisition targets to further increase their manufacturing capabilities. In 2019, Novartis completed their acquisition of French CDMO CellforCure; Thermo Fisher announced a $1.7 billion acquisition of Brammer Bio; Hitachi completed their acquisition of European CMO apceth; and Catalent acquired CMO Paragon Bioservices for $1.2 billion.

Smaller developers are also looking to expand their manufacturing capabilities earlier on in the development timeline. This year, Precision BioSciences opened the first in-house cGMP manufacturing facility dedicated to genome-edited allogeneic CAR-Ts in the US; gene therapy developer REGENXBIO announced a new manufacturing facility to be operational by 2021; Elevate Bio unloacked with $150 million to provide centralized R&D and manufacturing resources to a suite of cell and gene therapy companies; and Audentes, recently acquired by Astellas, announced the launch of their new cGMP plasmid manufacturing facility.

“Cell and gene therapy manufacturing will continue to play a prominent role in the sector as these therapies expand from orphan indications into indications with larger patient populations.”
Cell and gene therapy manufacturing will continue to play a prominent role in the sector as these therapies expand from orphan indications into indications with larger patient populations. When discussing the outlook for cell and gene therapies in the next decade, Sheila Mikhail, CEO of AskBio, said "I think there will be a lot of interesting developments as we move into pathway diseases, we have a lot of potential. AAV gene therapies for monogenetic diseases – we've made a great impact – but I think there's a lot more that will be happening outside of that space."

**THE OUTLOOK FOR 2020**

Looking forward in 2020, we expect many of these trends to continue. There is a strong demand for financing in the regenerative medicine sector globally; while the IPO market may continue to be constrained by US elections, financings prospects are generally strong.

As an increasing number of products are entering pivotal trials, we expect a large number of significant Phase 3 data readouts. The extensive late-stage progress in many clinical programs in 2019 is expected to translate to several regenerative medicine approvals worldwide in 2020; in particular, we expect the number of approved gene therapies to more than double over the course of the next one to two years. Researchers will continue to progress the technology forward, with advances expected in both viral and non-viral gene therapy delivery methods and in addressing immunogenicity for off-the-shelf therapies.

On the policy side, we have seen a lot of excitement and willingness from legislators and regulators to advance this sector and ensure patients can access these therapies. As an increasing number of products begin to come to market, however, it is essential that policymakers enact the systematic changes needed to allow patients timely access to safe and effective therapies. In particular, ARM has worked with CMS in the US, as well as payers in Europe, to identify barriers to patient access as well as potential solutions. This will almost certainly be an area of focus for all stakeholders this year. In the context of regenerative medicine, drug pricing legislation in the US in 2020 may enable value-based payment models.

Other expected policy activity in 2020 includes additional FDA enforcement activities against clinics advertising unapproved stem cell therapies (the period of enforcement discretion comes to end in November), increased international dialogue on point-of-care therapies, including the Hospital Exemption in the EU. ARM will continue to work with stakeholders to develop and promote the necessary policy frameworks for these innovative therapies.

Regenerative medicine is on the rise. The scientific, clinical, and financial milestones are the evidence of a strong and growing sector, bolstered by strong stakeholder support from not only industry experts, but regulators, providers, and patient advocates. With tens of thousands of patients poised to receive and benefit from regenerative medicines in the coming decade, it is vital that we continue to work to build the infrastructures necessary to develop, deliver, and reimburse these therapies."
necessary to develop, deliver, and reimburse these therapies. The past decade saw phenomenal advances in the science of regenerative medicine, and I am excited to continue to work with sector stakeholders in 2020 and beyond on the steps still needed to bring that amazing science to patients.

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AUTHORSHIP & CONFLICT OF INTEREST

Contributions: All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Acknowledgements: None.

Disclosure and potential conflicts of interest: The author has nothing to disclose.

Funding declaration: The author received no financial support for the research, authorship and/or publication of this article.

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Article source: Invited.

Revised manuscript received: Jan 27 2020;
Publication date: Jan 30 2020.