



Alliance *for* **Regenerative Medicine**



Quarterly Regenerative Medicine Sector Report

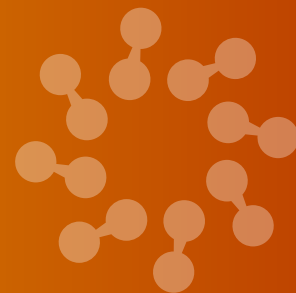


The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field.

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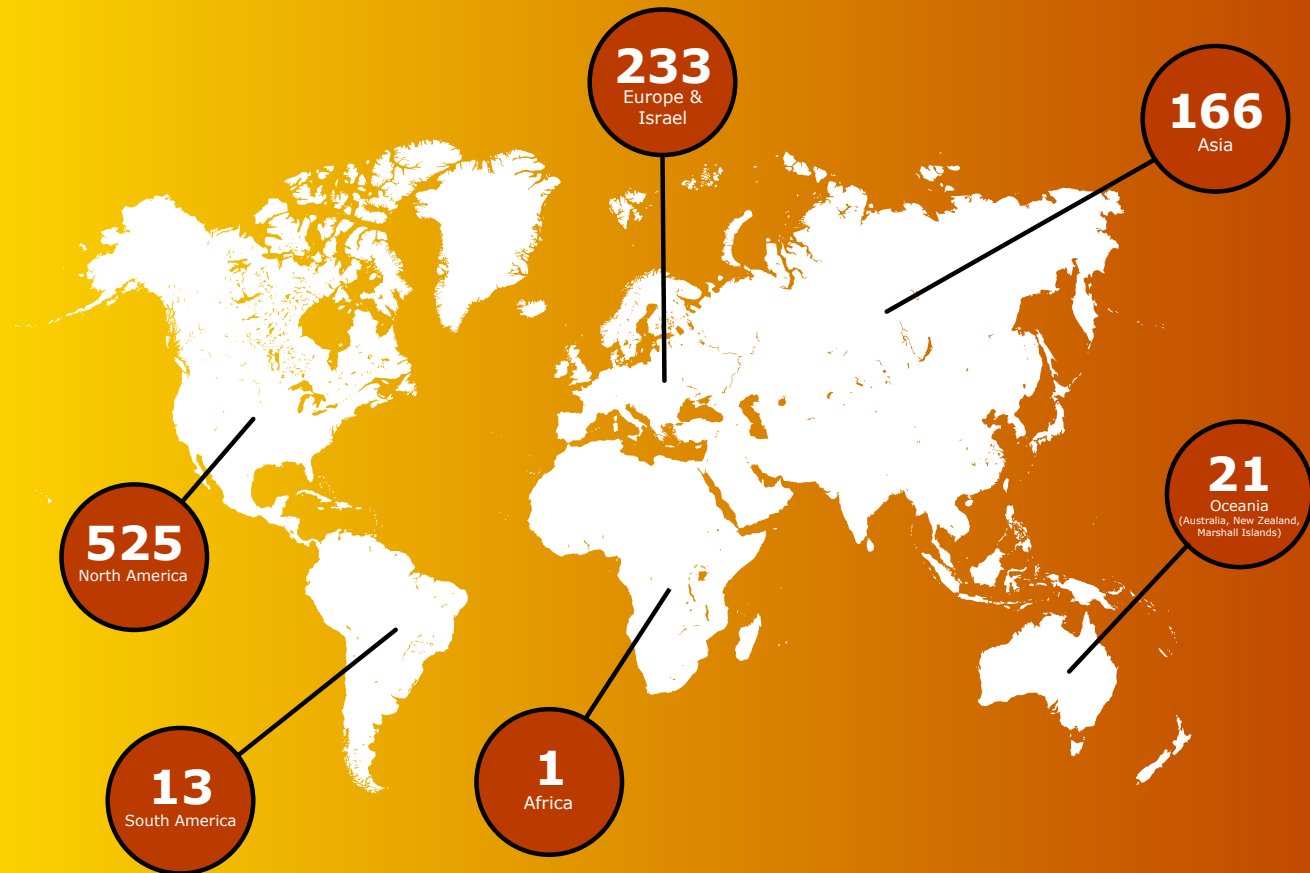
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Global Landscape

959+ Regenerative medicine companies worldwide, including gene therapy, cell therapy, and tissue engineering therapeutic developers



Companies by Technology:

*please note, individual companies may be active in more than one technology type



Gene Therapy: 461



Cell Therapy: 603



Tissue Engineering/
Biomaterials: 127

Industry Overview

The momentum of the regenerative medicine sector during the first half of 2019 continued into the third quarter, with a wide range of pipeline, policy, and dealmaking news.

On the policy front, several groups advocated for ethical gene editing practices. Through the publication of the Therapeutic Developers' Statement of Principles, ARM has established a bioethical framework for the use of gene editing in therapeutic applications. The World Health Organization's expert advisory committee approved the first phase of work on a new global registry of gene editing clinical trials, while U.S. Senators Dianne Feinstein, Marco Rubio, and Jack Reed called for international guidelines on the clinical use of germline editing.

Innovations in pricing and reimbursement continued. CMS issued a final national coverage determination of CAR-T therapies for Medicare beneficiaries in the U.S., as well as approved an increase to NTAPs (from 50% to 65%) for CAR-T therapies through 2020. Cigna launched the Embarc Benefit Protection plan, available to employers, HMOs, and other insurers, to fully cover the costs of Luxturna and Zolgensma initially, and possibly other gene therapies in the future. Outside of the U.S., Italy's AIFA and Novartis implemented a new outcomes-based payment model for Kymriah; the Scottish Medicines Consortium reversed its initial ruling and will now reimburse Kymriah in the DLBCL indication; and England's NICE recommended coverage for Luxturna.

The regenerative medicine pipeline yielded impressive preclinical and clinical data during Q3. Among those were positive preliminary results from Pfizer and Sangamo's Alta study of SB525 in hemophilia A, Amicus's data from seven Batten disease patients treated with AAV-CLN6, and GenSight's Phase III RESCUE trial follow-up, in which half of treated patients regained sight at 96 weeks. Notably, Editas and Allergan announced they will soon start enrolling patients in the first U.S. trial of an *in vivo* CRISPR therapy.

Dealmaking flourished in the third quarter. Following its initial investment in 2016, Bayer fully acquired allogeneic stem cell therapy company BlueRock Therapeutics for up to \$600M. Vertex made another significant acquisition, picking up Semma Therapeutics (stem cell-derived human islets for diabetes) for \$950M. Australia's Mesoblast took the opportunity to expand geographically and partnered with Germany's Grunenthal to develop its cell therapy for lower back pain in an alliance worth up to \$1.1B.

Financings were also abundant. Century Therapeutics launched with \$250M to develop allogeneic cancer cell therapies. Passage Bio, Nkarta Therapeutics, and Achilles Therapeutics each brought in \$100M+ Series B rounds, while publicly traded companies uniQure, Fate Therapeutics, Atara Biotherapeutics, and AVROBIO all raised significant follow-on financings.

The final quarter of 2019 is now upon us, with likely more exciting developments in this sector, including the U.S. and EU regulatory filing of BioMarin's valrox in hemophilia A. That filing is expected to be based off of a Phase I/II study showing durability of therapy for 3+ years, and a completed Phase III interim analysis. We'll keep a close eye on what the end of the year brings and how 2020 is shaping up.



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Financings



TOTAL Q3 2019 GLOBAL FINANCINGS

\$2.6 Billion raised in Q3 2019
7% decrease YoY from Q3 2018

\$7.4 Billion raised YTD 2019
32% decrease YoY from 2018



GENE & GENE-MODIFIED CELL THERAPY

\$1.3 Billion raised in Q3 2019
38% decrease YoY from Q3 2018

\$5.6 Billion raised YTD 2019
30% decrease YoY from 2018



CELL THERAPY

\$1.6 Billion raised in Q3 2019
13% decrease YoY from Q3 2018

\$3.3 Billion raised YTD 2019
48% decrease YoY from 2018



TISSUE ENGINEERING

\$40 Million raised in Q3 2019
327% increase YoY from Q3 2018

\$114 Million raised YTD 2019
86% decrease YoY from 2018

**Total amount raised represents sector-wide figures; please note that some companies utilize technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups.*

*** Figures do not include M&A transaction totals.*

Examples of Key Financings in Q3 2019

Public offerings:

- uniQure raises \$225M in follow-on public offering – September 4
- Fate Therapeutics raises \$173M in follow-on public offering – September 18
- Atara Biotherapeutics raises \$150M in follow-on public offering – July 18
- AVROBIO raises \$138M in follow-on public offering – July 19
- MeiraGTx raises \$75M in follow-on public offering – August 7

Corporate partnerships and other financings:

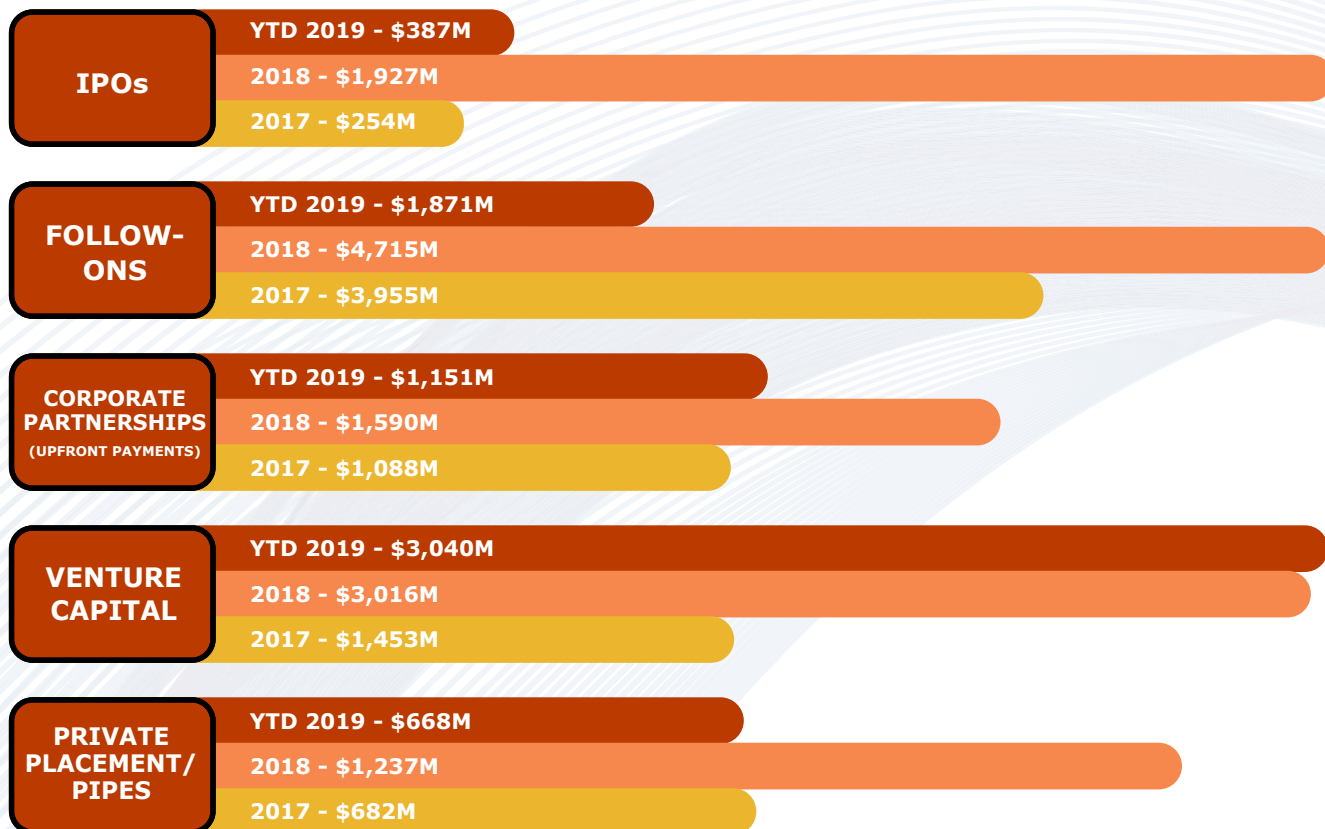
- Century Therapeutics launches with \$250M in venture financing – July 1
- Grünenthal and Mesoblast enter into \$150M upfront strategic partnership to develop and commercialize MPC-06-ID – September 9
- Achilles Therapeutics raises \$121M in Series B financing – September 3
- Nkarta Therapeutics raises \$114M in Series B financing – September 4
- Passage Bio raises \$110M in Series B financing – September 4
- Repare Therapeutics raises \$82M in Series B financing – September 4
- Oncorus raises \$80M in Series B financing – August 21
- Astellas Pharma signs \$80M upfront agreement with Frequency Therapeutics to develop and commercialize therapy for hearing loss – July 17
- Bellicum Pharma raises \$70M in private placement – August 16

Mergers & Acquisitions:

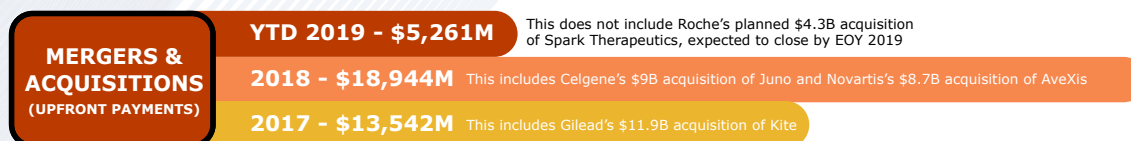
- Vertex Pharmaceuticals acquires Exonics Therapeutics for \$245M upfront – July 31
- Bayer acquires BlueRock Therapeutics for \$240M upfront – August 8

Financings

Total Global Financings by Type, by Year



Mergers & Acquisitions: Upfront Payments



Key

2019 YTD

2018

2017

Celebrating 10 Years

Commentary from ARM's Founding Members

In 2009, the regenerative medicine sector was still young — however, stakeholders already recognized the potential for this growing field to disrupt the traditional practice of medicine. In September of that year, co-founders Morrie Ruffin and Michael Werner launched the Alliance for Regenerative Medicine with 25 founding members, committed to promoting regulatory, research, and reimbursement policies that would foster innovation in the field.

Ten years later, ARM now has more than 350 members across 25 countries. The first gene therapy products have been launched in Europe, the United States, Canada, Japan, and Australia, with many additional products expected to come to market in the next few years. ARM frequently engages with the FDA and EMA on regulatory issues relating to the sector, and developers and payers are collaborating on a wave of innovative new payment models to ensure patients have access to these potentially lifechanging therapies.



Long before the cell therapy sector caught the attention of the entire medical community, ARM's founders were busy anticipating and addressing central issues facing the development of this new class of innovative therapies. Now, as the scientific, medical, and business communities continue to advance these complex and complicated therapies that offer promise for addressing countless unmet medical needs, ARM is paving the way by creating and promoting necessary learnings and tools; collaborating with via patient groups, academia, industry, investors, and other stakeholders; advancing process and product standards; promoting market and patient access; and garnering regulatory and policy support. It's hard to imagine the stunning pace of this sector's creation and growth without the thoughtful convening platform offered by ARM.

Today, with the cadence we are now experiencing in the sector, it's difficult to say if we are in the first chapter of the advanced therapies book — or the first paragraph of the first page. Regardless of where we may be now, our understanding of the serious and complex diseases to be treated, as well as the power of the cell and gene therapies we will develop, will fundamentally transform the health and longevity of human existence."

— Douglas Doerfler, CEO, MaxCyte



Ten years ago when the Alliance for Regenerative Medicine was formed, no one could have guessed that the regenerative medicine field would grow at such a fast pace. Now the promise for cures for patients with devastating diseases is right around the corner. ARM has played an instrumental role in this success by working with their members, policymakers, research institutions, and patient groups in moving this research forward. I believe the next 10 years will bring great discoveries in regenerative medicine, and I look forward to working with ARM as the leader and convener in this sector as the potential of regenerative medicine is realized."

— Dena Ladd, Executive Director, Missouri Cures

Celebrating 10 Years

Commentary from ARM's Founding Members



Since it launched a decade ago, ARM has been a leader in the industry. More than simply keeping pace, as some industry associations do, ARM has consistently driven advancements in the field by focusing on key bottlenecks limiting progress, providing reliable and valuable data for its members and others following the sector, and hosting events that have emerged as the most important networking/partnering events in the annual cycle.

Regenerative medicine is evolving rapidly, driven by transformational advances such as reprogramming and gene editing. ARM has been at the forefront of developing policy and ethical guidelines for these technologies, helping to ensure the industry is maintaining high standards and advocating for widespread adoption of cell and gene therapies. With a focus on manufacturing and patient access, it is clear that the industry has 'come of age' under the leadership and guidance of ARM."

— Michael May, *CEO, Centre for the Commercialization of Regenerative Medicine*



Over its 10 years of existence, it's an understatement to say that ARM has had a significant impact on the industry it serves. It has been an incredible experience to be part of the ARM journey, as well as a personal and professional honor to recently serve as its Chairman. Without the work of ARM in the formation of the ARM Foundation, the establishment of the Standards Coordinating Body, and its contribution to the 21st Century Cures Act, and more, regenerative medicine would not be where it is today — shifting the paradigm of medicine globally.

It is this foundation which we must leverage towards market access, improvements in the industrial infrastructure, and creating partnerships that extend the reach of ARM and its members. These opportunities for collaboration are available for us to seize, creating value not just for our individual organizations, but for the entire sector together. There has truly never been a more exciting time to be part of the regenerative medicine industry."

— Robert Preti, *CEO and President, Hitachi Chemical Advanced Therapeutic Solutions, LLC; General Manager, Hitachi Chemical Regenerative Medicine Business Sector*



Few advances have captured the imagination of the global healthcare community more than the regenerative medicine industry. Over the past 10 years, we've seen cell and gene therapies progress from interesting laboratory and clinical curiosities to what they've become today — plausible and promising therapeutic options for countless patients in need.

During that time, ARM has been a steadfast proponent of cellular and genetic medicines, supporting and educating the innovators, investors, legislators, and interested stakeholders from every part of the globe. The ARM community has become the authoritative voice of this quickly advancing field, providing confidence in the science and technology, guidance to the legislators and regulators, and hope to the patients and their families who just want a shot at a normal, healthy, and productive life."

— Phil Vanek, *General Manager, Cell and Gene Therapy Strategy, GE Healthcare*

Clinical Trials

1,052 Clinical Trials

Underway Worldwide by End of Q3 2019

Ph. I: 363 • Ph. II: 594 • Ph. III: 95

Number of Clinical Trials Utilizing Specific RM/AT Technology: Q3 2019



GENE THERAPY

Total: 370
Ph. I: 115
Ph. II: 223
Ph. III: 32



GENE-MODIFIED CELL THERAPY

Total: 418
Ph. I: 201
Ph. II: 201
Ph. III: 16



CELL THERAPY

Total: 218
Ph. I: 41
Ph. II: 147
Ph. III: 30

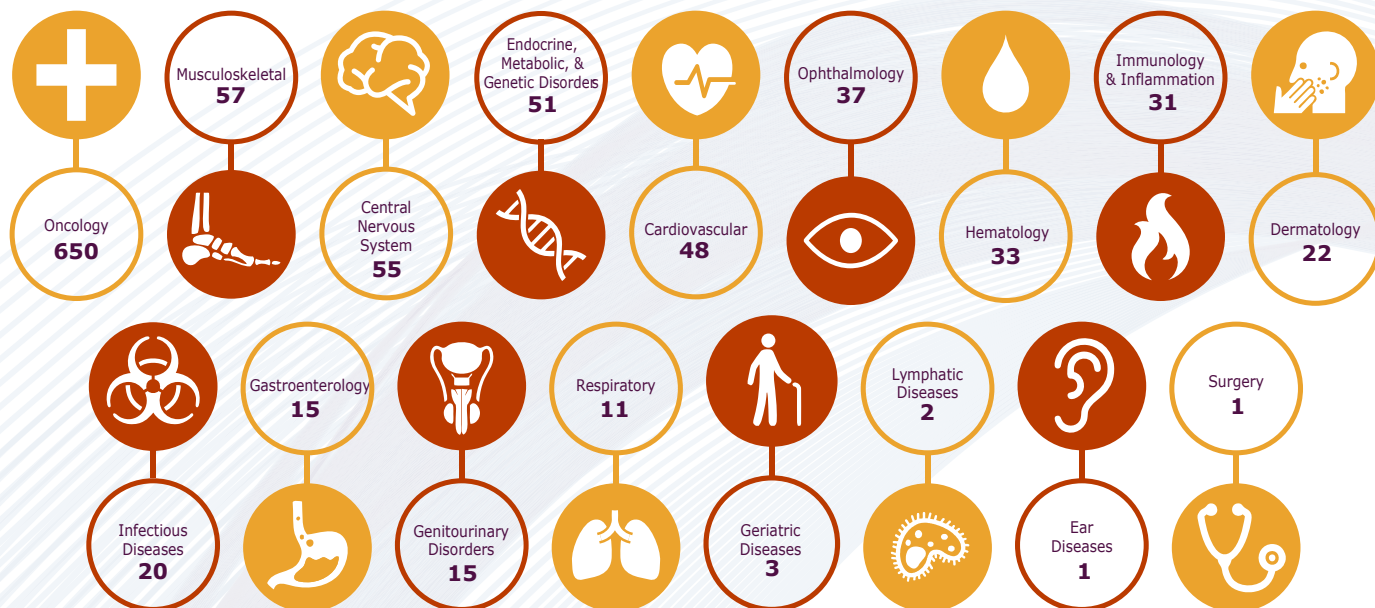


TISSUE ENGINEERING

Total: 46
Ph. I: 6
Ph. II: 23
Ph. III: 17

Clinical Trials

Clinical Trials by Indication: Q3 2019



- 650 (62%) of all current clinical trials are in oncology, including leukemia, lymphoma, and cancers of the brain, breast, bladder, cervix, colon, esophagus, ovaries, pancreas, and others.
- 57 (5%) are in musculoskeletal disorders, including muscular dystrophies, spinal muscular atrophy, osteoarthritis, degenerative disc disease, bone and cartilage defects, and others.
- 55 (5%) are in central nervous system disorders, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, traumatic brain injury, ALS, and others.

Select Significant Clinical & Data Events: Q3 2019

Gene Therapy & Genome Editing Programs

- GenSight Biologics reports sustained efficacy and safety at 96 weeks in RESCUE Phase 3 clinical trial of GS010 for the treatment of Leber hereditary optic neuropathy – September 23
 - » GS010-treated eyes regained more than two-thirds of the initial loss occurring in the most acute phase of the disease.
- AveXis presents new data from Phase 3 SPR1NT and STR1VE trials continuing to show significant therapeutic benefit of Zolgensma in patients with spinal muscular atrophy (SMA) Type 1 – September 19
 - » All 22 patients in the SPR1NT trial were alive and free of permanent ventilation. Patients with two copies of SMN2 achieved or maintained a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score of greater than 50, with five patients reaching the maximum score of 64.
 - » Eleven patients (50%) in the STR1VE-US study and two patients (6%) in the STR1VE-EU study achieved the ability to sit without support for at least 30 seconds according to Bayley-III Gross Motor criteria.
- bluebird bio presents updated data from the Phase 2/3 clinical study of their Lenti-D gene therapy for cerebral adrenoleukodystrophy – September 18
 - » Of those patients who have or would have reached 24 months of follow-up and completed the study, 88 percent (N=15/17) continue to be alive and MFD-free in a long-term follow-up study.
- CLS Therapeutics receives U.S. Orphan Designation for their CLS-014 gene therapy for the treatment of pancreatic cancer – September 18
- Ocugen receives U.S. Orphan Designation for their OCU400 gene therapy for the treatment of CEP290 mutation-associated retinal disease – September 18
- GeneTx and Ultragenyx receive U.S. Orphan Designation and Rare Pediatric Disease Designation for their GTX-102 for the treatment of Angelman Syndrome – September 3
- Mustang Bio and St. Jude Children's Research Hospital receive the FDA's RMAT designation for their MB-107 gene therapy for the treatment of X-linked severe combined immunodeficiency – August 22
- Ziopharm Oncology receives EMA Orphan Designation for their Ad-RTS-hIL-12 plus Veledimex for the treatment of glioma – August 8
- Orchard Therapeutics receives FDA RMAT Designation for their OTL-103 gene therapy for the treatment of Wiskott-Aldrich syndrome – July 29
- LogicBio Therapeutics receives Rare Pediatric Disease Designation for their gene-edited therapy LB-001 for the treatment of methylmalonic acidemia – July 16
- Prevail Therapeutics receives the FDA's Fast Track Designation for their gene therapy PR001 for the treatment of Parkinson's disease in patients with a GBA1 mutation – July 8

Select Significant Clinical & Data Events: Q3 2019

Cell-Based Immuno-Oncology Programs

- Adaptimmune receives U.S. Orphan Designation for their SPEAR T-cells targeting MAGE-A4 for treatment of soft tissue sarcomas – September 9
- CARsgen Therapeutics receives U.S. Orphan Drug Designation for their anti-BCMA autologous CAR-T therapy for the treatment of multiple myeloma – August 31
- Mustang Bio receives U.S. Orphan Drug Designation for their MB-102 CAR-T therapy for the treatment of acute myeloid leukemia – July 24

Cell Therapy Programs

- SanBio receives the FDA's RMAT Designation for its SB623 cell therapy for the treatment of chronic neurological motor deficits secondary to traumatic brain injury – September 19
- Magenta Therapeutics receives the FDA's RMAT Designation for its MGTA-456 cell therapy for the treatment of inherited metabolic disorders – September 4
- Sigilon Therapeutics receives U.S. Orphan Drug Designation for their SIG-001 cell therapy for the treatment of hemophilia A – August 27
- DiscGenics receives the FDA's Fast Track Designation for its cell therapy IDCT for the treatment of degenerative disc disease – August 26

Commentary: Progress and Innovation in the Regenerative Medicine Sector

Commentary from ARM's Meeting on the Mesa, held April 2–4, 2019



“We’re going to start to see more and more products reach market [...] We are on this essentially very steep portion of a growth curve.”

“Ultimately, we hope to bring these therapies to individuals in need sooner. We’re very committed to the development of gene therapies for patient populations of all sizes. [...] We want to encourage innovative product development, clinical trial designs. We realize we have to collaborate, we understand that we don’t have all the answers, we understand that this is a field in which we have to essentially hold on to our hats because things are changing so quickly [...] so we look forward to working with the sector.”

— Dr. Peter Marks, *Director, Center for Biologics Evaluation and Research, U.S. FDA*

Innovation Around Manufacturing Technologies

“The industry has matured to the point where everyone believes this can work and that it can be a new paradigm in medicine and treating patients that are really sick. Now, we’re migrating into the question of how can we make it. I see a lot of smaller companies willing to be innovative because there’s already the established players — which were small, and are now kind of the old guys, the established guys — so the younger, newer ones that come into this space now need to find better and faster ways to leapfrog what’s there. We have seen a lot of newer players come to us and say [...] let’s find new avenues to surpass what’s currently available. So I think we’re right now at the cusp of a more innovative paradigm.”

— Nina Bauer, Ph.D., *Chief Commercial Officer, FloDesign Sonics*



“I think the bias is to try and innovate internally. We all have great scientists working for our companies, we really believe we can push innovation forward, so I think that’s a natural place to start — but it can also sometimes be a little bit myopic. There are things that each organization is good at and sometimes you end up like a hammer looking for a nail [...] So I am a big proponent of partnership between organizations because you bring two points of view together. It could be a supplier/customer relationship, or it could take another form, but [...] I think there’s definitely a real need for that.”

— Jerry Keybl, Ph.D., *Head of Cell and Gene Therapy Manufacturing, MilliporeSigma*

Commentary: Progress and Innovation in the Regenerative Medicine Sector

"We do expect this field to evolve very fast [...] I think we also expect to see more collaboration, because the players in this field are still a lot of very small organizations, we have limited resources, and the companies need to focus on what they do well, their therapeutic products. We need collaboration to solve other problems and enable speedy innovation."

— Jian Irish, Ph.D., *SVP, Global Head of Manufacturing, Kite, a Gilead company*

A Look Into the Crystal Ball - What Does the Future Hold for Gene Editing?



"How will the technology evolve? I think the most important development will be delivery. It's about getting the editing to the right cell. Once that is unlocked, there are so many diseases we can interact with. And once you get within the cell, it's about how you deal with the DNA — do you cause a double stranded break, or can you integrate a new piece of DNA into the target, or can you simply mutate a base? There's work going on going across all of our laboratories and a large amount of work in academia just looking at different ways to edit that I think will become increasingly normal. If we all come back in 10 years, there won't be a discussion about whether it's CRISPR or ZINC fingers, it's will be about editing and showing a benefit to patients."

— Sandy Macrae, Ph.D., *President and CEO, Sangamo Therapeutics*

"I think there will be a convergence of using all these technologies — *in vivo* and cell-based — to treat disease. We spend a lot of time thinking about the disease that we're targeting. What are the best tools, the best approach, you know, the complexity of editing, knocking things out, knocking things in [...] I think the most exciting thing about all this is really being able to treat diseases and patients that we can't reach today."

— Cindy Collins, *President and CEO, Editas Medicine*

"We've been quite encouraged by the number of smaller countries in South America, Asia, those regions, that have actually encouraged us to come in and help teach their regulatory experts, regulatory scientists, regulatory policymakers on the whole field of genetic medicine [...] Those interaction are, I think, very encouraging because they want to get involved. They know that there's a potential significant benefit to their countries and their patient populations, but they don't have the sophisticated infrastructure to handle these types of advanced therapies as the more developed countries have. I think that's going to be an area in the next five to 10 years that we'll see a much greater explosion in terms of activity, because some rare diseases that are rare here in the U.S. or in Europe are not rare in Africa and they're not rare in Asia. I think that's going to be one of the dynamics of not just the regulatory policies but also business models and how we evolve in terms of delivery in these countries."

— Robert Smith, *SVP, Global Gene Therapy Business, Pfizer*

Current Regulatory & Legislative Priorities

Market Access

- Drive the adoption of new payment models and value-based reimbursements by U.S. public payers
- Remove/mitigate barriers to value-based payment in Medicare & Medicaid
- Achieve DRG/NTAP revisions in Medicare IPPS to enable adequate reimbursement for CAR-T
- Launch European market access expert recommendations with comprehensive communications campaign

Regulatory

- Drive FDA CMC-related guidance/regulation improvements through formal comments and direct interaction
- Improve and streamline ATMP clinical trial requirements in Europe through continued EC engagement on GMOs and a fuller articulation of other barriers and delays

Industrialization and Manufacturing

- Complete and launch the A-Gene case study-based guide to gene therapy manufacture
- Advance A-Cell case study-based guide to cell therapy manufacture



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