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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Table of Contents

2  Global Landscape
3  Industry Overview
4-5 Global Financings
6-9 Commentary: Investment Outlook for Regenerative Medicines
10-11 Clinical Trials
12-13 Major Milestones & Key Data Events
14 Current Regulatory & Legislative Priorities
Global Landscape

917+
Regenerative medicine companies worldwide, including gene therapy, cell therapy, and tissue engineering therapeutic developers

- 233 Europe & Israel
- 145 Asia
- 502 North America
- 13 South America
- 1 Africa
- 23 Oceania (Australia, New Zealand, Marshall Islands)
Industry Overview

The first quarter of 2019 has set the stage for a year of significant policy, regulatory, and commercialization changes in the regenerative medicine market.

International regulatory bodies made important strides in Q1 on the policy front. The FDA finalized two guidance documents on regenerative medicines, one of which now extends the definition of regenerative medicine to include qualifying gene therapies. The EMA published draft guidance on how ATMP sponsors should design development programs using a risk-based approach, and France’s regulatory body ANSM has opened up its experimental fast-track pathway for advanced therapies. In China, regulators issued draft regulations on gene editing in response to reports last November that a scientist had performed germline modifications on embryos resulting in the birth of twin girls.

Stakeholders have come together to devise ways to pay for transformative therapies and ensure patients have access to life-saving medicines. Installment payment plans for Zolgensma, Luxturna, and LentiGlobin (now called Zynteglo) are underway or in early discussions, linking payments to product effectiveness. CMS issued their draft national coverage decision on CAR-T therapies, recommending coverage with evidence development. The final analysis is due in May 2019.

Financing activity was strong, reflecting the bullish sentiments from investors and industry representatives at ARM’s annual Investor Day in New York on March 21. Among the bigger venture rounds were Passage Bio’s $116 million Series A financing and Beam Therapeutics’ $135 million Series B fundraising. Taking advantage of the still-open IPO window, Precision Bio completed a $126 million offering.

On the acquisitions front, Roche paid $4.8 billion for Spark Therapeutics, while Biogen spent $800 million on Nightstar Therapeutics. Bristol-Myers Squibb could become a major CAR-T player if its proposed $74B deal for Celgene goes through. Cell and gene therapy manufacturers were popular targets as companies expand their focus to include manufacturing, with the acquisitions of apceth (by Hitachi), Brammer Bio (Thermo Fisher), and GE Healthcare’s biopharma business (Danaher).

Novartis and Gilead added additional markets for their CAR-T therapies, with Kymriah approved in Japan and Yescarta approved in Canada. AnGes’s Collategene, a non-viral gene therapy, also received its first approval, in Japan, for critical limb ischemia.

As Q1 closed, bluebird’s Zynteglo received a positive opinion from the EU’s Committee for Medicine Products for Human Use for transfusion-dependent beta-thalassemia, with final EMA approval expected in Q2. The FDA, EMA, and Japan’s PMDA are also expected to release regulatory decisions regarding Novartis/AveXis’s Zolgensma for spinal muscular atrophy. There is much to be hopeful for as the sector enters Q2 2019, not least of which are the anticipated approvals of this next wave of gene therapies.

–Amanda Micklus
Senior Consultant
Pharma intelligence | informa
Global Financings

TOTAL Q1 2019 GLOBAL FINANCINGS
$2.2 Billion raised in Q1 2019
42% decrease YoY from Q1 2018

GENE & GENE-MODIFIED CELL THERAPY
$2.1 Billion raised in Q1 2019
32% decrease YoY from Q1 2018

CELL THERAPY
$822.8 Billion raised in Q1 2019
59% decrease YoY from Q1 2018

TISSUE ENGINEERING
$14.4 Million raised in Q1 2019
96% decrease YoY from Q1 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 Q1 2019

Public offerings:
- TCR2 Therapeutics raises $86.3M in initial public offering – February 19, 2019
- Axovant raises $40M in follow-on public offering – March 13, 2019
- Anchiano Therapeutics raises $30.5M in initial public offering – February 14, 2019
- Cellular Biomedicine Group raises $20.1M in follow-on public offering – March 25, 2019

Corporate partnerships and other financings:
- Adaptive Biotechnologies signs $300M upfront agreement with Genentech for the development of cell therapies for the treatment of cancer – January 4, 2019
- Maze Therapeutics raises $191M in venture financing – February 28, 2019
- Beam Therapeutics raises $135M in Series B Funding – March 6, 2019
- Passage Bio raises $115.5M in Series A Financing – February 15, 2019
- Neurocrine Biosciences and Voyager Therapeutics enter into $115M upfront agreement to develop gene therapy for Parkinson’s – March 12, 2019
- MeiraGTx and Janssen sign $100M agreement to develop gene therapies for inherited retinal disorders – January 31, 2019
Global Financings

Total Global Financings by Type, by Year

**IPOs**
- Q1 2019 - $117M
  - 2018 - $1,927M
  - 2017 - $254M

**FOLLOW-ONS**
- Q1 2019 - $67M
  - 2018 - $4,715M
  - 2017 - $3,995M

**CORPORATE PARTNERSHIPS (UPFRONT PAYMENTS)**
- Q1 2019 - $688M
  - 2018 - $1,563M
  - 2017 - $1,121M

"Upfront payments in Q1 2019 are already nearly half full-year 2019 totals"

**VENTURE CAPITAL**
- Q1 2019 - $985M
  - 2018 - $2,907M
  - 2017 - $1,451M

**PRIVATE PLACEMENT/PIPES**
- Q1 2019 - $356M
  - 2018 - $1,245M
  - 2017 - $689M

Mergers & Acquisitions: Upfront Payments

**MERGERS & ACQUISITIONS (UPFRONT PAYMENTS)**
- Q1 2019 - $62M
  - 2018 - $18,944M
  - 2017 - $13,540M

*This includes Celgene’s $9B acquisition of Juno and Novartis’s $8.7B acquisition of AveXis*

*Roche’s $4.8B acquisition of Spark Therapeutics and Biogen’s $800M acquisition of Nightstar Therapeutics are both expected to close in Q2 2019 and are not included in the Q1 M&A figure.*
Fireside Chat: What’s Next for Gene Therapy

“I think if you look at what’s coming along the lines there’s a lot of excitement in the field of genome editing and gene therapy combined with genome editing [...] If you look in laboratories, I think some of the exciting things are single nucleotide base editing technologies. There’s a lot of interest in doing this type of work [...] And finally, I just want to say that I think the human genome work is extremely exciting, although it’s ancillary to gene therapy [...] As the gene transfer technologies get better and as we understand what these do I think it’s going to open up whole other pathways to the treatment of other types of diseases.”

“From an in vivo point of view, I think there’s been outstanding results in the muscles. [...] I think the central nervous system is a target for which there’s a lot of potential to treat some pretty devastating disorders. [...] I think you’re going to see a resurgence of interest in using gene transfer to treat heart disease. There’s a number of both academic and commercial entities working on ways to transduce the heart. [...] The other area to keep in mind is the pancreas, there’s a lot of efforts right now and there’s a lot of data. You can use two genes that are relatively small and if you put them into the alpha cell of the islets they can be converted into beta cells, in both human islets as well as in mouse, and it’s been used to treat diabetes. [...] I think this is a target that you’re going to see people go after very soon.”

“I’m going to make one point that I think is important. I don’t think there’s ever going to be one vector that’s going to supplant all other vectors, one size will never fit all, that’s my prediction. I think you’re going to see different vectors for different opportunities, and there will probably be some changing of predominant vectors over time.”

“I think [in the five-year period] what you’re going to see and what’s really going to be exciting is the innovation and the science, advances in vectorology, advances in understanding how the vector and the host interact with each other to elicit these responses, and perhaps novel approaches to get around some of these immune response issues. I think in the ten-year frame you’re going to see things like a nucleotide base pair editing really starting to take more fruition. [...] There are going to be more complex ways to genome editing in the future, to do more sophisticated things, and I think these are the things you’ll start hearing about in the next five to ten years.”

-- Mark Kay, M.D., Ph.D., Dennis Farrey Family Professor, Departments of Pediatrics and Genetics; Associate Chair for Basic Research (Pediatrics), Stanford University
Commentary: Investment Outlook for Regenerative Medicines

From left to right: Moderator Reni Benjamin (Raymond James) and panelists Elona Baum (DEFTA Partners), Dennis Purcell (Aisling Capital), Patrick Rivers (Aquilo Capital Management), and Matthew Gline (Roivant Sciences).

Investment Outlook for the Cell & Gene Therapy Space

"You look at the technology, you look at the team. For me, the technology has to be a game changer, and I know it sounds trite because everyone says that, you want something that’s really going to make a difference, but we really do. I mean, that’s why say we’re in the bucket of advanced therapeutics because we’re looking to meet unmet medical needs. [...] So you get a sense of what we’re really looking for in terms of technology. But it’s the team that is really important. I used to think it wasn’t as important, but I think we need a really mature team that can show that they can raise money."

"I don’t think the sector is overcrowded and, okay, that’s it, let’s pack up our bags. I think it’s only just beginning, so I’m very bullish on the sector as a whole [...] I think there’s a lot more out there to get proved, and this technology is going to be solving unmet medical need. [...] I see what’s in the pipeline and I’m very excited."

-- Elona Baum, Managing Director, DEFTA Partners

"We have a very clear framework for the type of company that makes sense for us to invest in. [...] Box number one is, do you have a platform technology that is differentiated in some way? [...] It has to create repeatable assets, and we want to know if it can be used against different disease targets and different disease areas. The more breadth it has, I think, the better for us. We also really like companies that already have partnerships with large pharma or bigger biotech companies. That’s a really important criterion for us. There are a lot of tangible benefits that come from those types of business development transactions. [...] Those are two really important boxes for us. The other is that we want to invest in companies that are already well-financed. [...] We prefer companies who are raising money because they can and not because they have to."

"What’s different about our processes for selecting investments is that manufacturing is the most important variable, and to a much greater extent than with any other type of company. The first thing we’re going to ask is, what is your manufacturing set up? How scalable is it? What can you do yourself? What do you have to outsource? What are you doing in process development today versus what do you need to accomplish tomorrow and how is that vision to commercial scale going to materialize? Manufacturing becomes question one, two, and three when getting to know a gene therapy for the first time."

-- Patrick Rivers, Principal, Aquilo Capital Management
Commentary: Investment Outlook for Regenerative Medicines

Cell Therapy for Solid Tumors

“With solid tumors, some of the barriers we have to overcome include, first of all, making sure that the immune cellular therapy, whatever it may be, actually sees the cytokines that are being secreted by the tumor. [...] A second point is that the cells, the immune cellular therapy, has to be able to confront and overcome the barrier to actually enter the tumor. [...] Then finally, once the immune cellular therapy gets into the tumor, it has to overcome the multitude of forces that suppress the immune system within the tumor. All these factors are really unique in my view to solid tumors and not faced by cell therapy developers working in hematological tumors. [...] I am optimistic that there are going to be solutions to solving many of these problems.”

-- Kurt Gunter, M.D., Chief Medical Officer, Cell Medica

“If you can get cell therapy to work in an allogeneic format, then that’s ultimately what’s going to win because that will allow you to provide therapy for so many patients. As we think about solid tumors that are very common like colon cancers, lung cancers, ovarian cancers, things like that, we’ll need to have that scalability in order to provide therapy to those people in need.”

-- Christopher Haqq, M.D., Ph.D., EVP, Research and Development and Chief Scientific Officer, Atara Biotherapeutics
Gene Therapy Manufacturing

“It’s pretty simple. Clinical development timelines [for gene therapies] are very, very short compared to traditional development. Typically, you’re talking about four, four-and-a-half years from first-in-human to submission, which means that you have to think about the end game in terms of how you’re going to make the product almost before you dose the first patient. I think that mentality is a bit strange for people in traditional development [...] but if you don’t think about that from the point when you first dose, you’re going to be behind the eight ball.”

-- Paul McCormac, Ph.D., Category Lead Rare Disease, Biotherapeutic Pharmaceutical Sciences, Pfizer

“I think we need to take advantage of the fact that regulators are very open for us to actually move these things to the clinic. Some of the results are highly transformational – we’re getting RMAT designations, breakthrough therapy designations – of course, we have to figure out how to deal with that. So I think you actually have to think well before you dose your first patient how you’re going to get to commercial.”

-- Luis Maranga, Ph.D., Chief Technical Operations Officer, Voyager Therapeutics
Clinical Trials

1,060
Clinical trials underway worldwide by end of Q1 2019

Number of Clinical Trials Utilizing Specific RM/AT Technology: Q1 2019

Gene Therapy
Total: 372
Ph. I: 123
Ph. II: 217
Ph. III: 32

Gene-Modified Cell Therapy
Total: 374
Ph. I: 160
Ph. II: 197
Ph. III: 17

Cell Therapy
Total: 268
Ph. I: 55
Ph. II: 182
Ph. III: 31

Tissue Engineering
Total: 46
Ph. I: 11
Ph. II: 22
Ph. III: 13
• 618 (58%) 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.

• 67 (6%) are in cardiovascular disorders, including congestive heart failure, myocardial infarction, critical limb ischemia, heart disease, and others.

• 60 (6%) are in diseases of the central nervous system, including multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, traumatic brain injury, ALS, and others.
Gene Therapy & Genome Editing Programs

- Krystal Bio announced that the EMA has granted PRIME designation to their KB103 gene therapy for the treatment of epidermolysis bullosa – March 29, 2019

- Axovant reported positive data from the first cohort of their Phase II clinical trial of AXO-Lenti-PD gene therapy for Parkinson’s disease – March 11, 2019
  - Patients in the first cohort experienced an average UPDRS Part III (motor) OFF score improvement of 25 points at 3 months after administration of AXO-Lenti-PD, representing an average improvement of 42% from baseline.

- AnGes’s Colletagene gene therapy for the treatment of critical limb ischemia received preliminary approval in Japan – February 21, 2019

- Ocugen was granted FDA Orphan Drug Designation for their OCU400 gene therapy for the treatment of NR2E3 mutation-associated retinal degenerative disease – February 14, 2019

- uniQure announced updated clinical data from their Phase IIb study of AMT-061 in patients with hemophilia B – February 8, 2019
  - Mean FIX activity for the three patients at 12 weeks increased to 38% of normal, exceeding threshold FIX levels generally considered sufficient to eliminate or significantly reduce the risk of bleeding events.

- AVROBIO announced updated clinical data from the ongoing Phase I and Phase II studies for their AVR-RD-01 gene therapy for Fabry disease – February 6, 2019
  - All patients with reported data after dosing with AVR-RD-01 exhibited AGA plasma enzyme activity above the diagnostic threshold for classic Fabry disease at all timepoints measured in the two studies.

- REGENXBIO received FDA Rare Pediatric Disease Designation for their RGX-181 gene therapy for the treatment of the CLN2 form of Batten disease – January 31, 2019

- CRISPR Therapeutics and Vertex announced FDA Fast Track Designation for CTX001 for the treatment of sickle cell disease – January 4, 2019

- Ultragenyx announced positive topline results from the first cohort of their Phase 1/2 clinical study of DTX401 gene therapy in glycogen storage disease type Ia – January 4, 2019
  - The first patient in Cohort 1 had a clinically meaningful improvement in time to hypoglycemia from 3.8 hours at baseline to 7.7 hours at Week 12; patient 2 had a clinically meaningful improvement in time to hypoglycemia from 4.1 hours at baseline to 9.0 hours; patient 3 had an improvement in time to hypoglycemia from 5.4 hours at baseline to 6.5 hours at Week 12.

- Myonexus Therapeutics received FDA Orphan Drug Designation for MYO-102, an investigational gene therapy for alpha-sarcoglycanopathy (LGMD2D) – January 2, 2019
Major Milestones & Key Data Events

Cell-Based Immuno-Oncology Programs

- SOTIO announced from its Phase II trial of its DCVAC/OvCa dendritic cell vaccine in combination with standard chemotherapy in women with first relapse of platinum-sensitive epithelial ovarian cancer – March 19, 2019
  - The combination of chemotherapy and immunotherapy corresponded with 73% survival at two years, compared to 41% survival when chemotherapy was used alone.

- Gamida Cell presented new data from their ongoing Phase I study of NAM-NK in patients with non-Hodgkin lymphoma and multiple myeloma – February 21, 2019
  - The data demonstrated that NAM-NK was highly active, with three complete responses observed in patients with NHL and one complete response in a patient with MM.

- Novartis’s Kymriah received preliminary approval in Japan for the treatment of pediatric patients with relapsed/refractory B-cell acute lymphoblastic leukemia and adult patients with relapsed/refractory diffuse large B-cell lymphoma – February 21, 2019

- Autolus Therapeutics announced updated results from ongoing CARPALL trial of pediatric acute lymphoblastic leukemia – February 19, 2019
  - Twelve of 14 patients achieved a complete response. The median duration of remission in responding patients was 7.3 months with a median follow-up of 14 months. Five of 14 patients (37%) remain in CR with ongoing persistence of CAR-T cells and associated B cell aplasia.

- Kite/Gilead’s Yescarta received approval in Canada for the treatment of adults with relapsed/refractory large B-cell lymphoma – February 19, 2019

Cell Therapy Programs

- Gamida Cell presented initial data from its Phase I/II study of NiCord in severe aplastic anemia – February 21, 2019
  - The initial cohort of three patients successfully underwent a stem cell transplant consisting of NiCord plus a haploidentical stem cell graft, and experienced rapid engraftment, sustained hematopoiesis and accelerated immune recovery.

- ReNeuron presented positive data from its Phase I/II trial of its hRPC cell therapy candidate for the treatment of retinitis pigmentosa – February 20, 2019
  - All three of the first cohort of subjects in the Phase II part of the trial have reported a significant improvement in vision, on average equivalent to reading an additional three lines of 5 letters on the ETDRS eye chart.

- Asterias provided a top line 12-month data update for its OPC1 Phase I/IIa clinical trial in severe spinal cord injury – January 24, 2019
  - At 12 months, the average improvement in upper extremity motor score as measured by the International Standards for Neurological Classification of Spinal Cord Injury scale for Cohort 2-5 subjects was 8.9 points.
Current Regulatory & Legislative Priorities

**Regulatory**

- Promote clear, predictable, and efficient regulatory frameworks.
- Assess all FDA, EMA, and related guidance relevant to cell and gene therapy, including guidance related to manufacturing, CMC, and other industrialization issues.
- Promote international convergence of key regulation and guidance to promote global product development by identifying specific areas of regulatory inconsistency among jurisdictions and developing proposals for adoption by regulatory agencies.

**Reimbusement**

- Develop principles of ARM-endorsed global value framework.
- Develop strategies to remove or mitigate barriers via regulatory changes or legislation for public and private payers both in the U.S. and in key EU countries.
- Secure favorable access and reimbursement for RM / AT products.

**Industrialization and Manufacturing**

- Reduce standards, technical, and regulatory barriers to the scale up of RM / AT therapies.
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