Alliance *for* Regenerative Medicine

Advancing Gene, Cell, & Tissue-Based Therapies

2019

ARM Annual Report & Sector Year in Review

Alliance *for* Regenerative Medicine

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.

www.alliancerm.org

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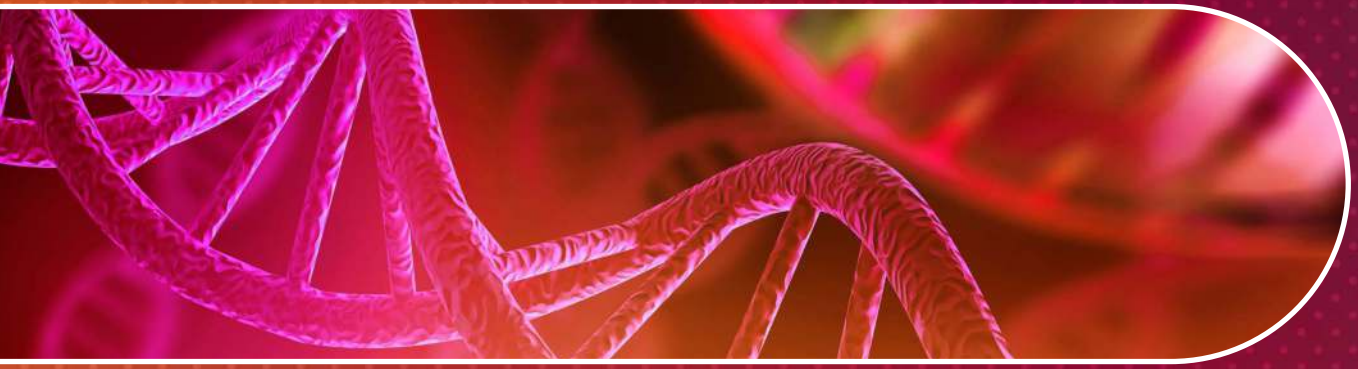


ARM Annual Report

2019 Global Regenerative Medicine Sector Overview


The Promise of
Advanced Therapies

Letter from the CEO

2019 was a great year in the cell and gene therapy sector, as well as for the Alliance for Regenerative Medicine (ARM). ARM's role as the convener and voice of the cell, gene, and tissue-based therapeutic sector continued to expand globally.

The number of approved products grew significantly, with gene therapies for spinal muscular atrophy (AveXis / Novartis's Zolgensma), beta thalassemia (bluebird bio's Zynteglo), and critical limb ischemia (AnGes's Collategene) receiving their first approval in the US, Europe, and Japan, respectively. CAR-T therapies received additional approvals in Canada (Kite / Gilead's Yescarta) and Japan (Novartis's Kymriah). In 2019, developers filed for marketing authorizations for 10+ regenerative medicines, many of which we expect to be approved in 2020. Within the next 1-2 years, the number of approved gene therapies is expected to double.

These approvals meant a growing number of patients suffering from a diverse array of serious diseases and disorders were able to receive transformative, innovative treatments. We estimate that 4,500 to 5,000 people have been treated with FDA and EMA approved gene therapies and gene-modified cell therapies, with thousands of additional patients benefitting from earlier cell and tissue products. The number of patients targeted for enrollment in regenerative medicine clinical trials has climbed to 60,000+ globally.

Here at ARM, the growth of the sector has supported terrific growth in our organization and activity. We now have more than 350 member organizations, and our collective work effectively addresses the key challenges to sustainable success in the sector:

- Achieving clear, predictable, and harmonized **regulatory** pathways
- Enabling effective market access and value-based **reimbursement** policies
- Overcoming **manufacturing** hurdles
- Conducting original sector **analysis, communication**, and policymaker **education**
- Facilitating sustainable **access to capital**

The following pages detail our activities in these areas as well as some of our key advocacy wins in 2019. But there is still much to do.

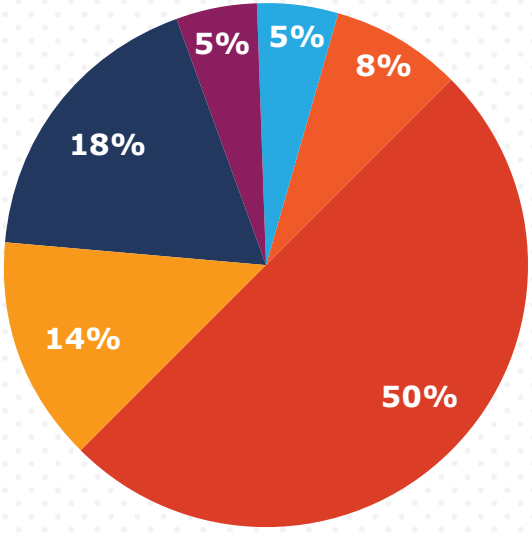
We're grateful for the support that the leading companies, research institutions, and patient advocates in the space have provided to ARM. We look forward to our ongoing engagement with legislators, regulators, and payers in the US and Europe.

Together, we're committed to ensuring that patients will be able to access these lifechanging, safe, and effective therapies.

Janet Lambert
Chief Executive Officer
Alliance for Regenerative Medicine

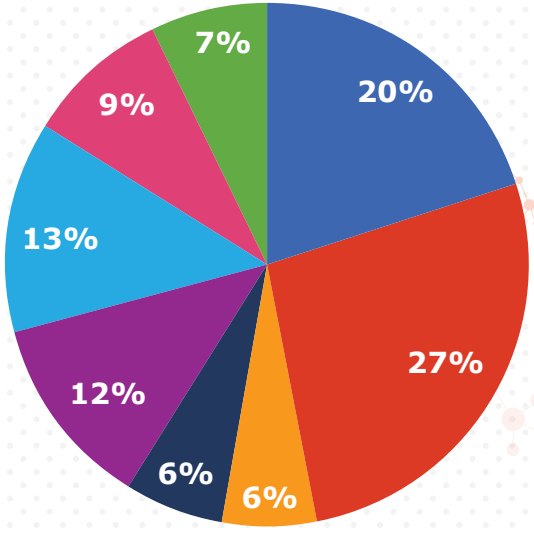
ARM Membership Report

ARM's membership has increased from 274 members at the end of 2017 to 350 members at the end of 2019. In 2019 alone, ARM membership grew by 15 percent.



Organization Type

- Corporations (Revenue > $50M)
- Corporations (Revenue < $50M, < 100 Full Time Employees)
- Corporations (Revenue < $50M, > 100 Full Time Employees)
- Non-Profit Institutions
- Academic Institutions
- Affiliates & Financial Institutions



Organization Focus

- Gene Therapy
- Cell Therapy
- Gene & Cell Therapy
- Tissue Engineering
- CMOs and CROs
- Service Providers
- Advocacy Organizations
- Research Organizations

ARM Members

As of the end of 2019:

4BIO Capital*
4D Molecular Tx
AABB
Abeona Tx
Accelerated Bio
ACF Bioservices
Adaptimmune
Adicet Bio*
Adverum Bio
AGTC
Aivita Biomedical*
Akouos*
Akron Bio
Albumedix
Aldevron
Alpha-1 Foundation
Ambys*
American Association of Tissue Banks
American Gene Technologies International
American Society of Plastic Surgeons
Amicus*
Andalusian Initiative for Advanced Therapies
ANEMOCYTE
Angiocrine Bio
apceth Biopharma*
Archbow Consulting*
Artiva Bio*
Aruvant*
Aseptic Technologies*
ASGCT
AskBio*
Aspect Biosystems
Asset Management Company
Association of Clinical Research Organizations
Astellas
Atara Bio
Athersys
Audentes Tx
AusBiotech
Autolus*
Avectas
Avery Tx
Avita Medical
AVM Bio
AVROBIO
AxoGen
Axovant
B-MoGen
Barkey*
Baylor College of Medicine
Be the Match Biotherapies
Bellicum Pharma
BioBridge Global
BioCardia
BioLife Solutions
BioMarin
BioStage
Biotech Mountains
Blood Centers of America
bluebird bio
BlueRock Tx
Bone Tx
BrainStorm Cell Tx
Brainxell
Brammer Bio
C3i
Cabaletta Bio*
Caladrius Bio
Capricor Tx
Cardinal Health
Caribou Bio
Carisma
Carpenter Consulting
Cartherics*
Celavie Bio*
Celgene (BMS)
CEO Council for Growth*
CGT Catapult
Cell Medica
Cellatoz*
CellCAN*
Cellect Bio*
CellGenix
Cello Health
CBMG*
Cellular Technology Limited
Celonic
Celsense
Center for the Advancement of Science in Space
CCRM
Century Tx*
Cevec*
Chemelot
CIRM
City of Hope
Cleveland Clinic
Cleveland Cord Blood Center
ClinicalMind
Coalition for Clinical Trials Awareness
Cobra Bio*
Cognate Bio
CombiGene
Cook Myosite*
Cornell University
Covance*
CRISPR Tx
Cryoport Systems
CSL
CTI Clinical Trial and Consulting Services
CureDuchenne*
Cynata Tx
Dark Horse Consulting
DiscGenics
EB Research Partnership
Editas Medicine
Elevate Bio*
Emerging Therapy Solutions*
Encoded Tx*
Enzyvant Tx
ERA Consulting
ESGCT
EVERSANA*
EveryLife Foundation for Rare Diseases
Evidera
ExCellThera
Exograders*
Falcon Tx
FARA
Fate Tx
Fibrocell Science
Fight Colorectal Cancer
Flexion Tx
Fondazione Telethon
Foundation for Biomedical Research and Innovation
Fraunhofer Institute for Cell Therapy and Immunology
Fred Hutchinson Cancer Research Center
Frequency Tx
Fresenius Kabi*
FUJIFILM Cellular Dynamics
G-CON*
GalbraithWight*
Gamida Cell*
GammaDelta Tx
GE Healthcare
GE2P2*
Gemini BioProducts*
Generation Bio*
GENETHON
Genprex*
GenSight Biologics
Gift of Life Marrow Registry
Gilead / Kite
Giner
GSK
Global Genes
GPB Scientific
Gyroscope Tx
Halloran Consulting*
Healios K.K.
Histogen
Hitachi Chemical Advanced Tx Solutions
Hogan Lovells
Homology Medicines
Humanscape*
Huron Consulting*
Hybrid Concepts International
ICON*
Immusoft
InRegen
InsightRX*
Intellia Tx
Invetech
Invitria
Invitrx
Iovance
IQVIA
ISCT*
ISSCR
IVERIC Bio
Johns Hopkins
Johnson & Johnson
Key Biologics
Kiadis Pharma
Kimera Labs*
Kytopen*
L7 Informatics*
LabConnect
Lake Street Capital Markets
Latham BioPharma*
LatticePoint Consulting
Legend Biotech
Locate Bio*
LogicBio
Lonza Biologics
Lovelace Biomedical*
Ludwig Boltzmann Institute
Lysogene
Magenta Tx
MaSTherCell
MaxCyte
MEDIPOST America
Medpace
MeiraGTx
MSK Cancer Center
Mesoblast Limited
MilliporeSigma
MiMedx
Minerva Bio
Miromatrix Medical
Missouri Cures
MolMed
Musculoskeletal Transplant Foundation
Mustang Bio
National Disease Research Interchange
National Multiple Sclerosis Society
National Stem Cell Foundation
Nebraska Coalition for Lifesaving Cures
Neural Stem Cell Institute
Neurogene*
New Jersey Innovation Institute
New York Stem Cell Foundation
NexImmune
NIIMBL*
Nkarta*
Northwestern University Comprehensive Transplant Center
Novadip Bio
Novartis / Avexis
Novitas Capital
Novo Nordisk*
NYBC*
Obsidian*
Odylia Tx*
Oisin Bio*
OncoSenX*
Opsis Tx
Orchard Tx
Organabio
Orgenesis
Orig3n
Oxford BioMedica
panCELLa
PPMD*
PDC*line Pharma SA
Pfizer
Pluristem Tx
PolarityTE
Polyplus-transfection*
Poseida Tx
Precigen*
Precision Bio
Prevail Tx*
Prevent Cancer Foundation
Project 8p*
Promethera Bio
PTC Tx*
Recardio*
Recombinetics*
Regenerative Patch Technologies
ReGenesys
Regeneus
REGENXBIO
REMEDI
ReNeuron
RepliCel Life Sciences
Rescue Hearing*
Rexgenero
Rigenerand*
Rocket Pharma
RoosterBio
Roslin Cell Therapies
Rousselot*
RxGen
SanBio
Sanford Health
Sanford Stem Cell Clinical Center @ UCSD
Sangamo Tx / TxCell
Sanofi / Bioverativ
Sarepta
Sartorius Stedim North America
SCM LifeScience
Scottish National Blood Transfusion Service
Semma Tx
Seneca Bio
Senti Bio*
Sentien Bio
Seraxis
Sigilon
Sirion Biotech*
Skyland Analytics*
SmartPharm Tx*
Solid Bio
Spark Tx
StafaCT*
Starfish Innovations*
STEL Technologies
StemBioSys
StemCyte
StemExpress*
Stempeutics*
Stop ALD Foundation
Student Society for Stem Cell Research
Synpromics
T-Knife*
Takeda*
Talaris Tx
Tenaya
TERMIS-Americas
Terumo BCT
Tessa Tx
Texas Heart Institute
The Michael J. Fox Foundation
Theradaptive*
Thermo Fisher Scientific
ThermoGenesis
TikoMed
Tmunity Tx
TrakCel
TreeFrog Tx*
Tremont Tx*
Trizell
Tulane University
UCSD Stem Cell Program
Ultragenyx
UMass Medical School
Unicyte
uniQure
Unite 2 Fight Paralysis
United Spinal Association of VA
Universidad de los Andes
University of Colorado
University of Pennsylvania
Unum Tx*
VERIGRAFT
ViaCyte
VidaCel
Videregen
Vigene*
VINETI
ViveBiotech
Vivet Tx
Voisin Consulting
Voyager Tx
WiCell*
WindMIL Tx
World Courier
Wuxi
Xintela
Xyphos Bio*
Yposkesi
Zelluna
Ziopharm Oncology*

*New to ARM in 2019

Letter from ARM Chairman Matthew R. Patterson

As I reflect on my first year as Chairman of ARM, I continue to be amazed by the incredible period of growth we are experiencing in the field of regenerative medicine. It is truly inspiring to think about what this growth means for the many patients and families around the world who are impacted by the serious conditions our treatments hope to address.

It is also remarkable to see the growth of ARM in 2019. ARM continues to be the convening force for the many stakeholders in our field, whose voices are critical in communicating the transformative value of the innovation our industry is creating. I continue to be passionate about the important role ARM plays in bringing these various parties together — whether it be manufacturers, academia, or patient groups — with a focus on advocacy with regulators, government and policy makers on the issues that will ensure our therapies successfully make it to the patients who need them.

As I enter my second year as Chairman, I am excited about the opportunities that lie ahead. But also know there remain significant challenges to be solved. I am confident we can overcome these barriers through continued conversation and collaboration, not just at our meetings throughout the year but also by sharing regular information, insights and thought-provoking analysis to keep our key stakeholders informed, connected, and prepared for the continued relentless pace of scientific and commercial progress we are seeing.

We have a lot to do and our sense of urgency could not be stronger. I am honored to help lead ARM through this critical period and look forward to working together with you in the coming year.

Matthew R. Patterson
Strategic Advisor
Audentes Therapeutics, an Astellas company

ARM's 2020 Board of Directors

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Chairman and Co-CEO
Pluristem Therapeutics

Usman 'Oz' Azam, M.D.
President and CEO
Tmunity Therapeutics

Rita Balice-Gordon, Ph.D.
Global Head, Rare and Neurologic Diseases Therapeutic Area
Sanofi

Ronald Bartek
Co-Founder and President
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MilliporeSigma

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Janssen R&D,
Janssen Pharmaceutical Companies of Johnson & Johnson

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GlaxoSmithKline

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bluebird bio

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AGTC

Jason Wertheim, M.D., Ph.D.
Edward G. Elcock Professor of Surgical Research and Associate Professor,
Division of Transplantation
Northwestern University

Special thanks to 2019 Board Members Flagg Flanigan (CEO and Chairman, DiscGenics), Michael May (CEO, Centre for the Commercialization of Regenerative Medicine), Keith Thompson (CEO, Cell and Gene Therapy Catapult), and Phil Vanek (General Manager, Cell and Gene Therapy Strategy, GE Healthcare) for their time on the ARM board.

Advocacy Successes in 2019

In 2019, ARM worked to improve the regulatory and legislative environment for regenerative medicines and ATMPs. In the United States, ARM engaged in discussion with the FDA, CMS, ICER, and Congress on issues including reimbursement for CAR-Ts, implementing value-based payment models in Medicaid and Medicare, and the use of real-world evidence in the approval process. In Europe, ARM worked with multiple stakeholders at the national and pan-European level, and published two original analytical reports on key policy issues: one on **patient access to ATMPs** as well as one on **trends in ATMP clinical development**. These reports provided recommendations on improving the environment for these ATMPs and the goal posts for our advocacy efforts moving forward.

2019 saw notable progress for ARM and for the reimbursement of cell and gene therapies. ARM helped to **secure language in the US Senate Finance Committee's drug pricing bill** that would allow state Medicaid programs to enter into pay-for-performance arrangements for certain gene therapies for the first time. ARM's advocacy work also contributed to the first ever **increase in a New Technology Add-On Payment**, which raised reimbursements for hospitals providing CAR-T therapies.

On the regulatory side, ARM worked with FDA to **successfully drive the refinement of CMC guidance** for regenerative medicines and to develop indication-specific guidances for gene therapy development. In Europe, ARM continues to drive simplification and harmonization of GMO requirements and to narrow the use of the hospital exemption. ARM was **invited to present** at an October 2019 meeting of the International Coalition of Medicines Regulatory Authorities (ICMRA), where ARM CEO Janet Lambert identified potential regulatory barriers to the development of and access to cell and gene therapies.

As the recognized policy voice of the sector, ARM filed 17 formal comments and letters with policymakers in the US and EU in 2019 to improve the regulatory and reimbursement environment for regenerative medicines.

Dr. Guido Rasi, Executive Director of the European Medicines Agency (EMA), keynotes ARM's inaugural Meeting of the Med in Barcelona, Spain — April 2019

Dr. Peter Marks, Director, Center for Biologics Evaluation & Research (CBER), US FDA, provides an update on the agency's strategies for advancing the development of gene therapies at ARM's Meeting on the Mesa in Carlsbad, CA — October 2019

US Advocacy Emphasizes Market Access, FDA Engagement

"The regulatory environment for gene and cell therapy has evolved rapidly over the years and we are appreciative of FDA/CBER's efforts to clarify requirements to support development of these products. The ARM regulatory committee has served as a close partner and collaborator to the Agency in ensuring our committee perspective is heard and represented in FDA's policies. Overall, we have been pleased with this partnership and look forward to continued collaboration with the Agency in support of advancing the field of gene and cell therapy."

— Adora Ndu, VP, Regulatory Affairs; Policy, Research, Engagement, & International, BioMarin; Co-Chair, US Regulatory Committee, ARM

Left: ARM meetings with top FDA officials at official liaison meeting — March 2019; Right: Dr. Anna Kwilis (FDA) present at ARM's annual CMC summit — December 2019

ARM members meet with Senator Bill Cassidy (R-LA), one of ARM's 2019 Legislator of the Year Awardees, to discuss value-based payment reform and the New Technology Add-on Payment program during ARM's annual Fly-In — May 2019

"We are already seeing the transformative potential of gene therapy treatment options for patients following the FDA approvals of Zolgensma and Luxturna, which are reshaping the way patients live. As the pipeline of gene and cells therapies matures and more options become available to patients, ensuring broad access to these treatments will be critical. ARM was an important early voice in assessing payment and financing challenges that could hamper adoption of gene and cell therapies while also advocating for critical and time sensitive solutions like payment tied to performance. Much work remains to convince Congress and other stakeholders to reform current reimbursement laws and policies to facilitate payment for life-altering therapies, and ARM continues to elevate the conversation around access with key stakeholders including the government, private sector and patients."

— Francesca Cook, MPH, Senior Director, Pricing and Market Access, REGENXBIO; Co-Chair, US Regulatory Committee, ARM

Cara O'Neill (left), Chief Scientific Officer of the Cure Sanfilippo Foundation and mother to a daughter with Sanfilippo syndrome, and Kristin Smedley (right), President of the Curing Retinal Blindness Foundation and mother of two sons affected by CRB1 retinal disease, present at ARM's DC Policy Forum — May 2019

"With an increasing number of cell and gene therapies coming to market in the US, it's essential that we establish appropriate reimbursement mechanisms for cell and gene therapies. To that effect, ARM will continue to prioritize the removal of barriers to innovative financings models in the US and globally. ARM will continue to advocate for the adoption and expansion of the language in the Senate Finance Committee's drug pricing bill that would enable state Medicaid programs to establish pay-for-performance models for gene therapy for the first time. ARM's "**Transformative Therapy Value Model for Rare Blood Diseases**," released in January this year, underscores our commitment to educating policymakers and other stakeholders regarding the immense value these therapies represent to patients and to the healthcare system as a whole. We also look forward to continuing our engagement with FDA on key issues in the sector, including 'sameness' in regards to the Orphan Drug Designation, early engagement with FDA in the development process, and US-EU regulatory convergence."

— Robert Falb, Director, US Policy and Advocacy, ARM

More than 70 congressional staffers, policymakers, and other sector stakeholders attend a Capitol Hill briefing entitled "The Gene Therapy Revolution — Delivering Promise to Patients," co-hosted by ARM, BIO, and Parent Project Muscular Dystrophy — May 2019

Accelerating ATMP Development, Patient Access in Europe

"2019 was another very successful year for the ARM European Regulatory Affairs Committee, with a strong focus on EU clinical trials and the international convergence of key regulation and guidance. In 2020, we look forward to further interacting with regulatory authorities, including at national level, to further improve and streamline the approval process for clinical trials in Europe ahead of the implementation of the new clinical trial regulation. The committee will also continue to propose recommendations and support the development of guidance to address some of the outstanding challenges for ATMP manufacturers, especially in areas such as product quality (CMC) and the European GMO legislation."

— Patrick Ginty, Head of Regulatory Affairs, Cell and Gene Therapy Catapult; Co-Chair, European Regulatory Affairs Committee, ARM

Clinical Trials in Europe — Recent Trends in ATMP Development

This report, released in October 2019, analyzes recent trends in new ATMP clinical trials in Europe. ARM provides recommendations to improve and accelerate the process to approve clinical trial applications to ensure Europe remains competitive in attracting new ATMP clinical development.

"ARM's recently-published analysis of trends in ATMP clinical development in Europe has provided great opportunities to engage with regulators on reducing approval timelines and streamlining processes, particularly for multinational trials. ARM has provided significant contributions to consultations on EMA regulatory guidelines on key topics in the European ATMP sector, including investigational ATMPs, genetically modified cells, the use of registries, and the EMA regulatory strategy to 2025. In addition, an analysis on the hospital exemption implementation was carried out and will be published in 2020, as well as a position paper on this topic."

— Annie Hubert, Senior Director, European Public Policy, ARM

Getting Ready for ATMPs in Europe – Recommendations for Timely Access to Transformative Therapies

Released in July 2019, the 'Getting Ready' report provides recommendations to ensure appropriate assessment and reimbursement of ATMPs in Europe, ensuring that patients can access safe and effective therapies as quickly as possible.

ARM CEO Janet Lambert speaks with payers, regulators, industry, and members of the media at a stakeholder event on patient access to ATMPs in Europe — December 2019

"The release of ARM's 'Getting Ready' report in 2019 was an important step in identifying barriers to patient access to ATMPs in Europe, and to identifying and implementing appropriate solutions. Following our multi-stakeholder event in Brussels at the end of last year, ARM is planning on furthering our analytical, policy, and adovcacy work promoting patient access and addressing topics including cross-border healthcare, modernization of ATMP frameworks, developing real-world-evidence infrastructures, and creating country-level recommendations to improve timely access to ATMPs."

— Paolo Morgese, Director, European Market Access, ARM

Scientific and Technological Leadership

ARM provides a convening forum for scientific and technological experts as the sector looks to advance cell and gene therapy manufacturing, progress next-generation technologies, establish standards and best practices, and collaborate with regulators on CMC requirements.

In 2019, ARM hosted meetings on comparability in cell and gene therapy manufacturing and CMC preparedness. ARM published a **commentary article** in *In Vivo* on manufacturing in May, and **co-hosted a webinar** with Informa on the topic in June. Work progressed on A-Gene and A-Cell — case study-based manufacturing best practices documents for the development of gene and cell therapies, respectively. Those documents are expected to be released in 2020.

Members of ARM's Science & Technology committee attend a workshop co-host by ARM and the US Pharmacopeia on comparability for cell and gene therapies, featuring presentations from the FDA and the European Committee on Advanced Therapies — May 2019

Robert Preti (President & CEO, Hitachi Chemical Advanced Therapeutics Solutions), Stewart Abbot (COO & CSO, Adicet Bio), Usman Azam (President & CEO, Tmunity Tx), Tim Lu (Co-Founder & CEO, Senti Bio), Bastiano Sanna (CEO, Semm Tx), and Dan Shoemaker (CSO, Fate Tx) discuss the impact of iPSCs on the cell therapy industry at ARM's Meeting on the Mesa — October 2019

More than 100 industry representatives and sector stakeholders attend ARM's 3rd annual CMC Summit. Dr. Anna Kwilas (Division of Cellular and Gene Therapies, CBER, FDA) and Dr. Veronika Jekerle (Specialized Scientific Disciplines Department, EMA) give presentations on their agencies' respective strategies for CMC preparedness in regenerative medicine — December 2019

"Importantly ARM has sharpened its focus to include the priority manufacturing issues facing the industry through its working committees and conferences that bring together industry leaders and regulatory agencies to work on solutions together. This is a primary reason GSK is a member as it helps us keep a leadership position in the field."

— Joe Tarnowski, Cell and Gene Therapy Platforms, Medicinal Sciences and Technology, R&D Division, GlaxoSmithKline (GSK)

"With a growing number of patients positioned to benefit from regenerative medicine, stakeholders must address potential barriers in manufacturing and scale up. ARM is actively working with the FDA on these issues, and ARM member input is helping to shape regulatory policy in this area — for example, in the six guidances for gene therapy released by the FDA earlier this year. In 2020, ARM will continue to facilitate progress in the areas of manufacturing and CMC requirements, workforce development, and international regulatory convergence. We look forward to continuing our manufacturing workshop series; the release of A-Gene, a first-of-its-kind case study-based reference guide on the best practices for the development of gene therapies; and furthering our work on A-Cell, a companion project to A-Gene focusing on cell therapies."

— Michael Lehmicke, Director, Science & Industry Affairs, ARM

ARM also worked to advance an international dialogue on gene editing. In August 2019, 13 leading therapeutic developers active in gene editing signed a **Statement of Principles**, asserting that germline modifications are currently inappropriate for in-human use. Since then, two additional signatories have been added. ARM was invited into discussions with the World Health Organization, and presented at a meeting of its advisory committee on oversight for clinical gene editing.

The Statement of Principles has been signed by:

AUDENTES THERAPEUTICS · bluebirdbio · BlueRock Therapeutics · CARIBOU BIOSCIENCES · CASEBIA · CRISPR THERAPEUTICS · editas MEDICINE · GENCURE · HOMOLOGY Medicines, Inc. · Intellia THERAPEUTICS · LogicBio therapeutics · Pfizer · PRECISION BIOSCIENCES · Sangamo THERAPEUTICS · TMUNITY

"We are delighted to have worked with our sector peers and alongside ARM to agree to these common principles and standards as we look to establish best practices and uphold the highest standards whilst developing these exciting technologies. As therapeutic developers utilizing gene editing technologies, we must ensure that our efforts, above all else, are carried out in a safe and ethical matter."

— Sandy Macrae, M.B., Ch.B., Ph.D., Chief Executive Officer, Sangamo Therapeutics

ARM Events Bring Leaders Together

ARM's events bring together industry leaders, investors, policy makers, clinicians, and patient advocates to network, partner, and learn about the latest clinical and commercial successes and challenges facing the sector. ARM's **Meeting on the Mesa** — which has become the world's premier regenerative medicine-focused event — attracted more than 1,200 attendees this past year. And ARM's inaugural **Meeting on the Mediterranean**, held in Barcelona, Spain, convened 400+ attendees in its first year.

In addition to these conferences, ARM also hosted a policy forum and legislative fly-in in Washington, DC, a State of the Industry briefing during JP Morgan Healthcare Conference, a regenerative medicine-focused investor event; and several receptions and smaller meetings in 2019. These events will continue to grow going into 2020.

In 2019, ARM held the inaugural Meeting on the Mediterranean, modeled after the highly successful Meeting on the Mesa. More than 400 attendees gathered in Barcelona to discuss the unique opportunities and challenges for regenerative medicines in Europe — April 2019

"ARM's inaugural Cell & Gene Meeting on the Mediterranean brought together the best aspects of ARM's two previous European annual meetings, providing a single forum to discuss industry-related topics as well as interact with the European investor community. This well-attended meeting convened key players in the European ATMP sector and beyond, highlighting the clinical, financial and policy outlook for the sector in Europe."

— Michael Hunt, CFO, ReNeuron

Left: Representatives of ARM member organizations gather at a welcome reception during ARM's 10th annual Meeting on the Mesa; Right: A full house as CBER Director Peter Marks discusses the FDA's approach to gene therapy on Day 2 of the meeting — October 2019

SAVE THE DATE

ARM'S UPCOMING EVENTS

CELL & GENE MEETING ON THE MEDITERRANEAN
BARCELONA, SPAIN
APR 15-17

MAY 19-20
DC POLICY FORUM & LEGISLATIVE FLY-IN
WASHINGTON, DC

ARM RECEPTION @ BIO
SAN DIEGO, CA
JUN 8

OCT 14-16
CELL & GENE MEETING ON THE MESA
CARLSBAD, CA

8th ANNUAL CELL & GENE THERAPIES STATE OF THE INDUSTRY BRIEFING
SAN FRANCISCO, CA
JAN 11

Stakeholder Educaton and Sector Data

The regenerative medicine sector is growing rapidly. Through a partnership with Informa, ARM curates a unique database of regenerative medicine therapeutics developers, financings, and clinical trials globally. Publicly available **global sector reports**, released quarterly, showcase growth and progress in the sector, and ARM data is often cited in news articles, market reports, and presentations on the regenerative medicine sector.

Left: ARM CEO Janet Lambert provides an overview of the clinical pipeline and financial landscape for the regenerative medicine sector at ARM's annual State of the Industry briefing during the JP Morgan Healthcare Conference.

In 2019, ARM launched three new **'indication-specific' reports**, providing a deep dive on regenerative medicine approaches to treat rare diseases, inherited blood disorders, and cancers.

In addition, ARM produced its first **country-specific report**, looking at the UK's regenerative medicine sector, in collaboration with the UK BioIndustry Association (BIA). The report was used in discussions with MHRA, NHS, and UK Parlimentarians regarding ATMP policies. ARM plans on producing additional indication- and country-specific reports in 2020.

UK report launch event – July 2019

"ARM is the trusted source of intelligence and data in the dynamic space of regenerative medicine. Their quarterly data reports provide financing, company dynamics, and clinical trial pipeline information in a synthesized format that is both visually appealing and easy to consume. This data, and other data that ARM distributes, is incredibly valuable for someone like myself to have access to, as I'm tasked with keeping a pulse on the cell & gene therapy market in my organization. ARM is thorough and transparent in their findings, which is what sets them apart from most other data suppliers. They also have unique relationships with key stakeholders in the space, which enables ARM to provide rich commentary and color that few others have insight to."

— Caroline Rand, Strategic Marketing Leader, Cell & Gene Therapy, GE Healthcare

Publicly Available Resources

Visit [redacted] to access additional resources, including:

- Quarterly global sector reports and other ARM publications
- Upcoming near-term clinical trial milestones & data readouts
- Access to slides, graphics, and figures from ARM presentations
- Our weekly sector newsletter, a robust round-up of business, clinical, scientific, and policy news in the sector
- Commentary from experts in the field

For questions about these and other available resources, please contact Kaitlyn Donaldson Dupont, Coordinator, Communications, at kdonaldson@alliancerm.org

ARM Foundation *for* Cell & Gene Medicine

The ARM Foundation is an independent, 501(c)(3) non-profit organization established by ARM in 2018 and dedicated to providing the education, information, and research needed to accelerate patient awareness of and access to these transformative therapies.

The Foundations three main projects are:

- **Gene Medicine Education Program:** A multi-year effort to provide the public with accurate, jargon-free information about the science, benefits, and limitations of therapeutic gene medicine technology.
- **Health Economic Impact Project:** The foundation is developing, with outside experts, advanced economic simulation models of regenerative medicines in several major disease areas to quantify the value of curative therapies compared to the current standard of care.
- **Industrialization of Cell and Gene Therapies:** This project will identify and prioritize the infrastructure, logistics, and healthcare system requirements essential to support widespread adoption of these transformative medicines.

"Gene medicine will achieve its vast potential only when the public, patients, and caregivers understand and accept it as a safe and effective therapeutic option."

— Stewart Parker, Board Chairperson, ARM Foundation

Special Thanks

We would like to extend a special thanks to ARM's member committees, task forces, and advisory committees, whose time and support make the work we do here at ARM possible:

Member Committees

Capital Formation Committee
Cell Therapy Interest Group
Communications and Education Committee
European Market Access & Value Committee
European Regulatory Affairs Committee
European Advanced Therapies Committee
Gene Therapy Interest Group
Government Relations Committee
Patient Engagement Committee
Science and Technology Committee
Tissue Engineering and Biomaterials Interest Group
US Market Access and Value Committee
US Regulatory Affairs Committee

Advisory Committees

Cell Therapy Advisory Committee
Gene Editing Task Force
Gene Therapy Advisory Committee
Tissue Engineering and Biomaterials Advisory Committee

For more information about ARM and how to get involved, please contact Alyce Osborne, Director, Member Engagement at aosborne@alliancerm.org.

ARM's 2020 Priorities

US Policy & Advocacy

- Remove and mitigate barriers to federal and state adoption of payment-over-time and outcome-based agreements for ATMPs
- Work with CMS at the federal level to ensure the appropriate reimbursement of CAR-Ts and other innovative therapies
- Drive effective CMC guidance refinement
- Maintain an appropriate regulatory framework for somatic genome editing

European Policy & Advocacy

- Gain better ATMP access conditions in Germany, France, the UK, and Italy
- Limit the growth and use of Hospital Exemption and other regulatory carve outs that threaten patient safety
- Streamline ATMP clinical trial requirements, particularly those related to GMO requirements

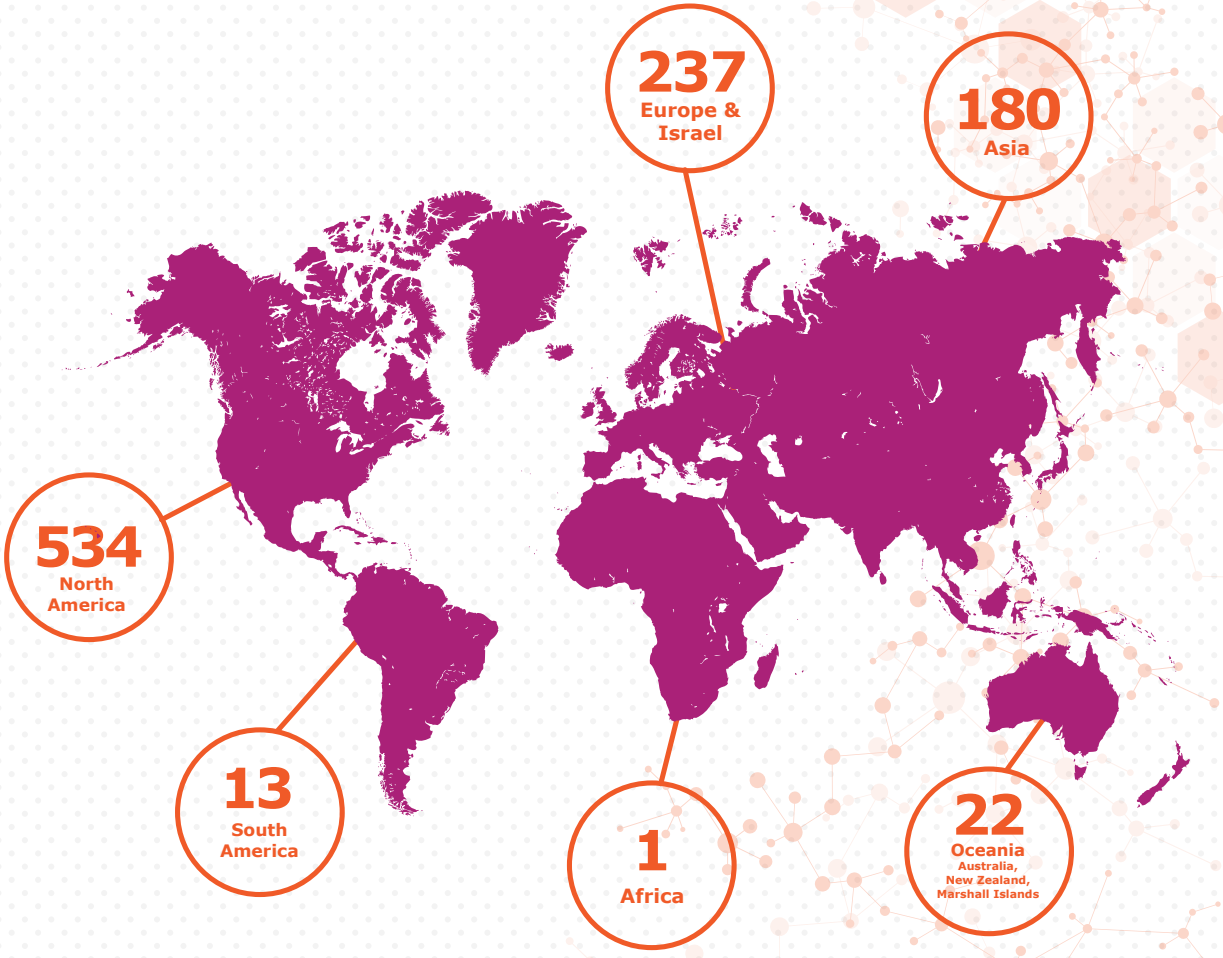
Science & Technology

- Complete and release A-Gene and A-Cell, ARM's collaborative manufacturing best practices guides for gene therapies and cell therapies, respectively
- Lead FDA engagement on key sector issues, including CMC guidance gaps, the use of induced pluripotent stem cells (iPSCs), and virus testing
- Represent the industry and patient view in the global gene editing dialogue

Global Regenerative Medicine Sector Report

Global Sector Landscape

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



Gene therapy: 496	Cell therapy: 625	Tissue engineering / biomaterials: 133

*Some companies active in more than one technology area.

Q4 2019 Summary Overview

With 2019 all wrapped up, the regenerative medicine industry can celebrate many achievements from the past year, not least of which was the approvals of three new therapies in the gene therapy sector (Zolgensma, Collategene, and Zynteglo), impressive clinical data, big deals, and innovations in pricing and reimbursement that are continuing to ensure that patients have access to these critical products. Before we move ahead, let's reflect on the exciting news and events of the final quarter of 2019.

On the commercial and pricing front, ICER developed a new value assessment framework for one-time/curative therapies to be implemented in 2020. In Q4 Novartis reported that Zolgensma's Q3 sales, the first full period on the market, exceeded analyst expectations, setting up the product for one of the strongest launches of a gene therapy to date. Novartis also announced an expanded access program for Zolgensma whereby it will offer up to 100 doses for free per year in countries where the product has not yet been approved.

Pharma and biotech companies also announced major US and EU first-time regulatory filings, including Gilead/Kite Pharma's KTE-X19, BioMarin's valrox, Bristol/Celgene's lisocabtagene, Orchard's OTL-200, and FerGene's nadofaragene firadenovec.

Fourth quarters are usually busy dealmaking periods, and Q4 2019 did not disappoint. Astellas paid $3 billion for Audentes Therapeutics, a transaction whose discussions began at ARM's Meeting on the Mesa in October 2019. Roche finally closed its acquisition of Spark Therapeutics, gaining US and UK regulatory clearance. Roche also signed the biggest gene therapy partnership of the year, worth nearly $3 billion, licensing ex-US rights to Sarepta's lead Duchenne muscular dystrophy therapy SRP-9001. At ARM's State of the Industry Briefing in January 2020, Lambert highlighted that regenerative medicine financings reached $9.8 billion in 2019, the second-highest level since the organization began tracking those figures. Q4 featured several big fundraises, including $100 million for eGenesis, a $274 million public offering for CRISPR Therapeutics, and over $570 million in investments in FerGene.

Other Q4 highlights included a paper on a new form of gene editing called prime editing that could expand the number of diseases addressed; the first two patients who received CRISPR gene editing (Vertex and CRISPR's CTX001) for sickle cell disease and beta thalassemia benefitted from therapy and only had temporary and treatable side effects; and significant investments announced by Harvard/MIT, Gilead, Fujifilm, and Thermo Fisher in manufacturing capabilities.

Like other sectors, there were ups and downs. MolMed withdrew Zalmoxis from the EU market due to commercial reasons. And He Jiankui, a professor from China Southern University of Science and Technology who conducted a gene editing experiment leading to the birth of the world's first gene-edited babies, was sentenced to fines and jail time.

As the world now moves into a new decade, the treatment paradigm for several diseases is likely to shift, where the administration of cell, gene, and tissues therapies will become more commonplace. We look forward to the advancements that 2020 will bring.

Amanda Micklus
Senior Consultant
Informa Pharma Consulting
Pharma intelligence | informa

Global Financings

2019 was the second strongest year for regenerative medicine financings to date.

TOTAL 2019 GLOBAL FINANCINGS
$9.8 Billion raised in 2019

GENE & GENE-MODIFIED CELL THERAPY
$7.6 Billion raised in 2019

CELL THERAPY
$5.1 Billion raised in 2019

TISSUE ENGINEERING
$442 Million raised in 2019

*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 2019:

Public Offerings

- CRISPR Therapeutics raises **$274M** in follow-on offering – November 19
- uniQure raises **$225M** in follow-on offering – September 4
- Fate Therapeutics raises **$173M** in follow-on offering – September 18
- Atara Biotherapeutics raises **$150M** in follow-on offering – July 18

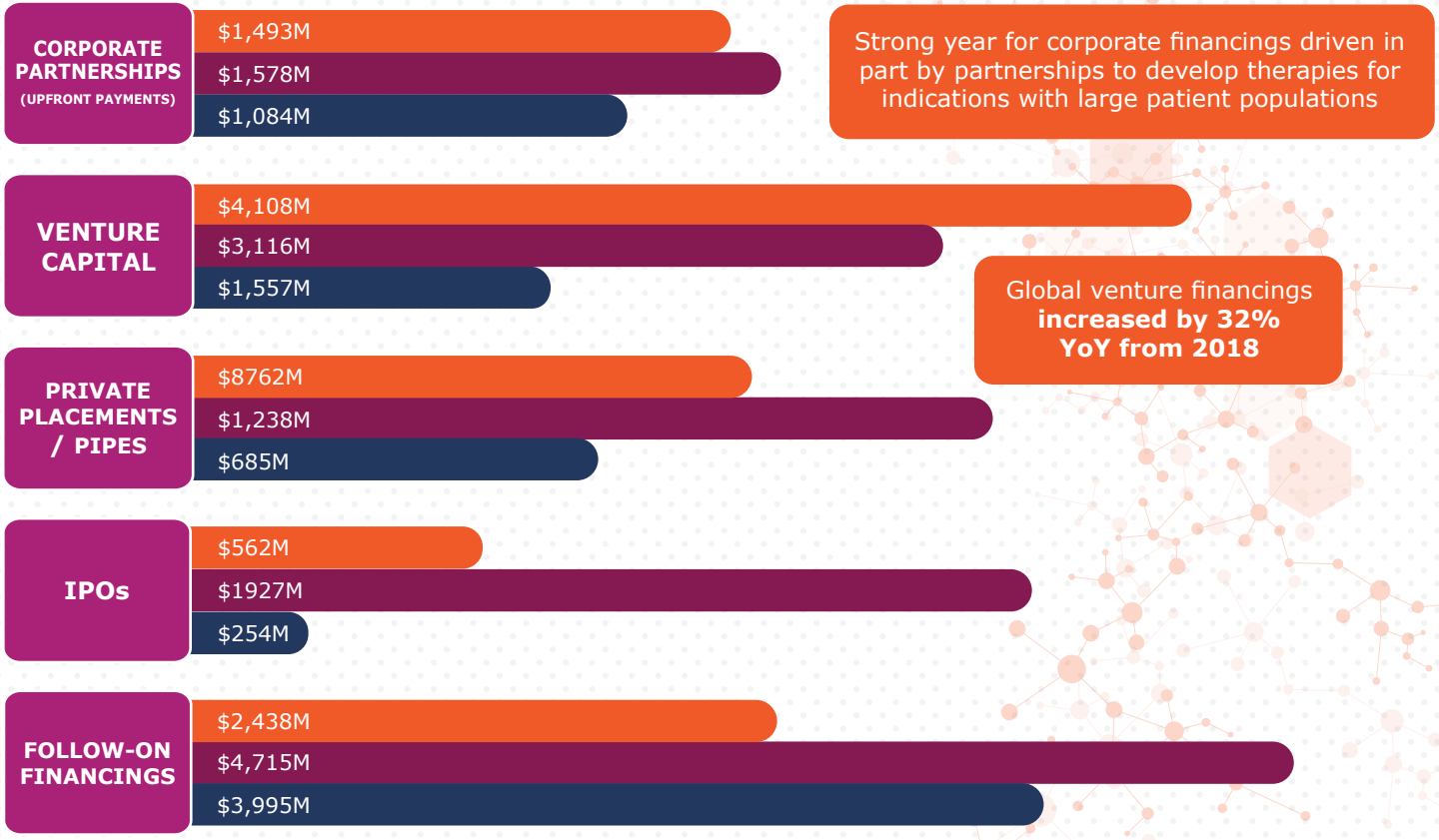
Corporate Partnerships & Other Financings

- Adaptive Bio and Genentech enter into **$300M** upfront agreement to develop personalized cellular therapies for cancer – January 4
- Century Therapeutics raises **$250M** in venture financing – July 1
- AskBio secures **$235M** in private equity – April 11
- Maze Therapeutics raises **$191M** in venture funding – February 28
- CRISPR Therapeutics and Vertex expand collaboration agreement with an additional **$175M** upfront to develop gene-edited therapies to treat muscular dystrophies – June 6
- Mesoblast signs **$150M** upfront agreement with Grunenthal to develop cell therapies for the development of cell therapies to treat lower back pain – September 10

Mergers & Acquisitions

- Roche acquires a 100% stake in Spark Therapeutics for **$4.8B** – December 17
- Thermo Fisher announces **$1.7B** acquisition of Brammer Bio – May 1
- Catalent acquires 100% stake in Paragon Bioservices for **$1.2B** – May 20
- Biogen acquires Nightstar Therapeutics for **$877M** – June 7
- Smith & Nephew acquires Osiris Therapeutics for **$661M** – April 17
- Vertex acquires a 100% stake in Exonics Therapeutics for **$245M** upfront – July 31
- Bayer acquires remaining stake in BlueRock Therapeutics for **$240M** upfront – August 8
- Sarepta acquires Myonexus Therapeutics for **$165M** upfront – April 4

Total Global Financings by Type, by Year



Strong year for corporate financings driven in part by partnerships to develop therapies for indications with large patient populations

Global venture financings **increased by 32% YoY from 2018**

Mergers & Acquisitions: Upfront Payments

Large and mid-cap pharmaceutical companies continue to ramp up activity in the cell and gene therapy sector with acquisitions of cell and gene therapy developers

LEGEND

- 2019
- 2018
- 2017

* 2019 figure does not include Astellas Pharma's $3B acquisition of Audentes, which closed in Q1 2020. The 2018 figure includes Celgene's $9B acquisition of Juno Therapeutics, and the 2017 figure includes Gilead's $11.9B acquisition of Kite Pharma.

ARM's 2020 State of the Industry Briefing

Usman "Oz" Azam, President & CEO, Tmunity Tx (moderator)

From left to right: Samarth Kulkarni, CEO, CRISPR Tx; Pascal Touchon, CEO, Atara Bio; Matt Kane, CEO & Co-Founder, Precision Bio; Claudia Mitchell, Senior VP, Product & Portfolio Strategy, Astellas

Emerging Cell Therapies

"What's been so impressive is the uptake of these new therapies, given all of these pressures and questions about access. Why is that? It's the response rates you're seeing for with late-stage cancers that have progressed despite trying all the other therapies. That's what makes this field exciting. […] I think that's why we're all here today and why we're so optimistic. Going into 2020, we have a new set of questions to start to answer and unravel in terms of how we can make these products more accessible."

— Matthew Kane, CEO & Co-Founder, Precision Biosciences

"We are privileged to be in this time when we're coming up with these new therapies. You know, one hundred years ago cancer was all about surgery. […] Then we had an era of very toxic chemo agents to try to kill these cancers, and that took years and decades. Then we had an era where antibodies and targeted agents really showed some hope. But now we're entering a phase of cell therapies – and I would argue that cell therapies are here to stay in cancer. […] For liquid tumors, I would argue that in the next five to six years, we're going to see at least a third of the market be cell therapies."

— Samarth Kulkarni, CEO, CRISPR Therapeutics

"We are delivering product today in our clinical trials and compassionate use programs in three days, just the shipping time from inventory to the patient. And I think that's really what we're here for in the allogeneic field."

— Pascal Touchon, CEO, Atara Biotherapeutics

From left to right: Timothy Miller, President & CEO, Gene Therapy Newco (moderator); Laurence Cooper, CEO, Ziopharm; Emile Nuwaysir, President & CEO, BlueRock Tx; Tim Lu, Co-Founder & CEO, Senti Bio; Shelia Mikhail, CEO, AskBio

Next Generation Cell & Gene Technologies

"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."

— Tim Lu, Co-founder & CEO, Senti Bio

"We're all preparing for a day when we can move away from the monogenetic diseases and make our technologies available for patients with Parkinson's, Alzheimer's — the potential is there, the science will work, it's just a matter of how we drop the cost of goods."

— Shelia Mikhail, CEO, AskBio

"What I'm most excited about in the field for engineered cell therapy was published just a few months ago by one of our peers, Fate Therapeutics. They showed you could use a pluripotent master cell bank to make an authentic cell, that you could make an NK cell that was of equivalent functionality to a cell that you'd harvested from the body. […] It's profound because I think it harkens to the end of harvested cell therapy. […] If you can make an NK cell that in vivo, in a human being, works just as well as a harvested cell — or better — I think you've reached a sea change in the industry, in the paradigm for how to make a cell therapy."

— Emile Nuwaysir, President & CEO, BlueRock Therapeutics

Global Clinical Landscape

1,066

Clinical Trials Underway Worldwide at the End of 2019

Ph. I: 381
Ph. II: 591
Ph. III: 94

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

Gene Therapy

Total: 352
Ph. I: 111
Ph. II: 209
Ph. III: 32

Gene-Modified & Cell-Based IO

Total: 452
Ph. I: 222
Ph. II: 215
Ph. III: 15

Cell Therapy

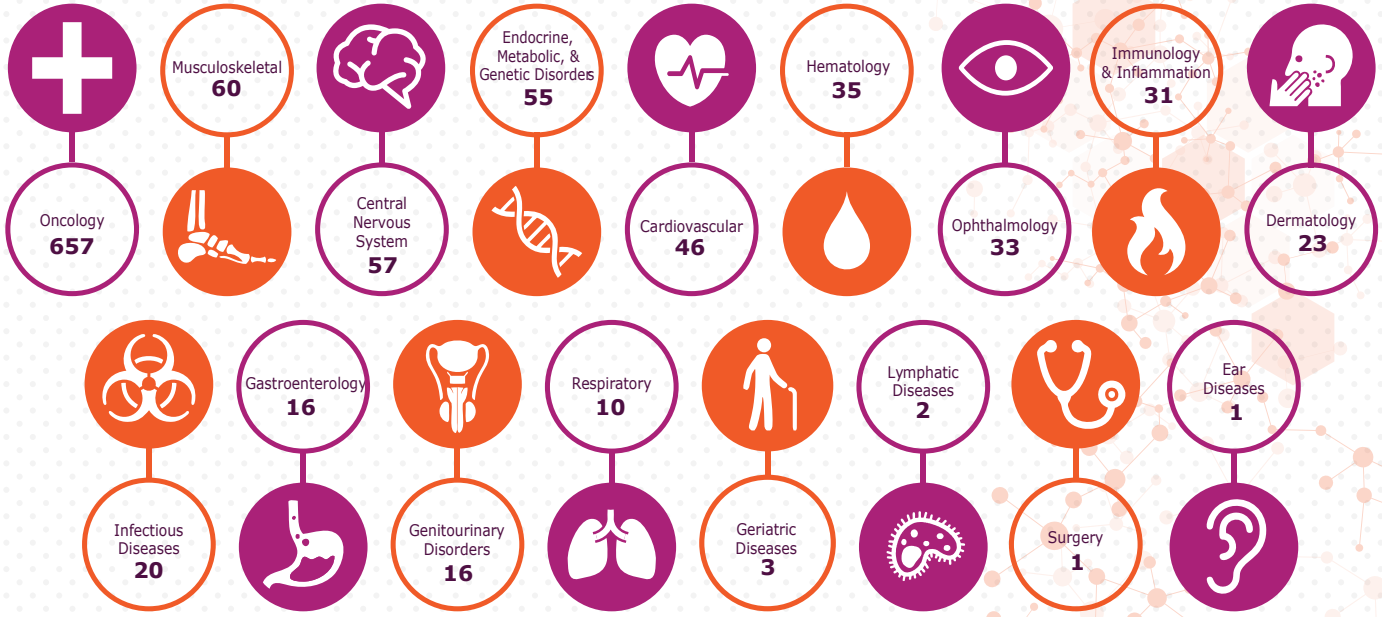
Total: 216
Ph. I: 42
Ph. II: 144
Ph. III: 30

Tissue Engineering

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

Within the last three years, there has been an explosion of early-stage clinical activity in gene-modified and cell-based immunooncology (IO), which now makes up about 58% of Phase 1 trials. These cell therapies achieved a number of significant milestones in 2019 as well. Fate Therapeutics, Precision Biosciences, and Cellectis all entered the clinic with allogeneic CAR-T therapies in hematological malignancies. In addition, gene-modified and cell-based immunotherapies are poised to expand to indications outside of oncology — in 2019, Cartesian initiated the first clinical trial for an autoimmune disorder, and Sangamo Therapeutics received UK authorization to begin a clinical trial of their CAR-Treg product to prevent immune rejection following kidney transplantation.

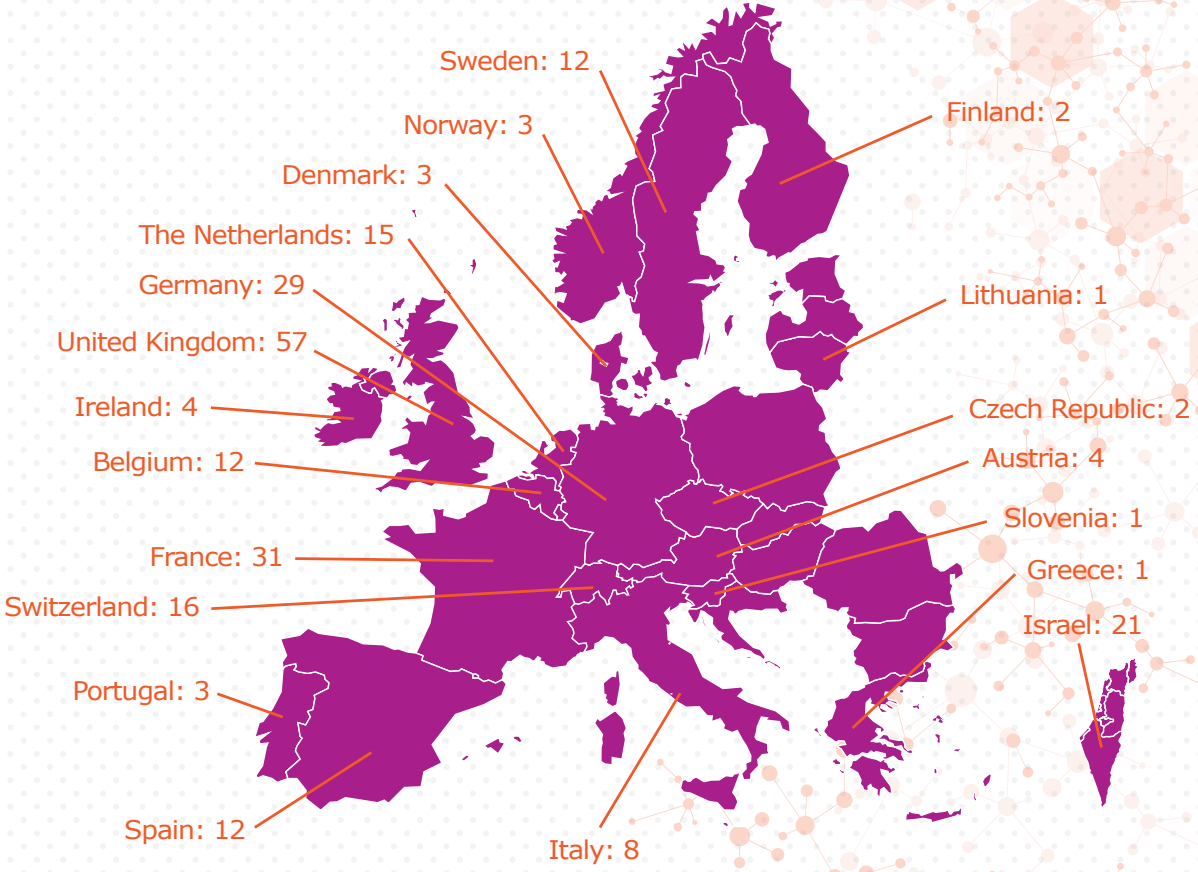
Clinical Trials by Indication: 2019



657 (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.

European ATMP Sector Overview

237+ **Regenerative medicine / advanced therapies companies based in Europe and Israel**



Gene therapy: 109

Cell therapy: 142

Tissue engineering / biomaterials: 39

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

2019 EUROPEAN/ ISRAELI FINANCINGS
$3.0 Billion raised in 2019
(appx €2.7 Billion)

GENE & GENE-MODIFIED CELL THERAPY
$2.2 Billion raised in 2019
(appx €2.0 Billion)

CELL THERAPY
$1.7 Billion raised in 2019
(appx €1.5 Billion)

TISSUE ENGINEERING
$154 Million raised in 2019
(appx €140 Million)

Despite YoY decreases in global financings, financings from regenerative medicine companies headquartered in Europe were on par with 2018, with a 3% YoY increase in total financings across technology types.

*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.
**Deals counted involve at least one European or Israeli company and include industry-funded deals only

Clinical Trials Sponsored by a European or Israeli Therapeutic Developer

260
Clinical Trials Underway
By End of 2019

Ph. I: 52
Ph. II: 161
Ph. III: 47

- Half (51%) of all European or Israeli clinical trials are in oncology, including leukemia, lymphoma, glioblastoma, melanoma, myeloma, and cancers of the cervix, ovaries, prostate, and colon, among others.
- 8% focus on endocrine, metabolic, and genetic disorders, including mucopolysaccharidosis types I, II, IIIA, and IIIB, Crigler Najjar syndrome, X-linked myotubular myopathy, and others.
- 7% focus on hematological disorders, including hemophilia, beta thalassemia, sickle cell disease, Fanconi's anemia, and others.

Commentary: Developing Regenerative Medicines for Indications With Large Patient Populations

"Gene therapy and stem cell-derived cell therapies represent two, distinct approaches for the development of new approaches to treat disease and genetic disorders. As powerful as these approaches are alone, together they offer even greater promise to treat a wide range of life-threatening diseases. By the use of gene editing technology, a form of gene therapy, cells derived from pluripotent stem cells can be engineered to deliver unique therapeutic benefits to patients. These specialized cells could be used to replace missing or defective cells, or they could be engineered to provide unique therapeutic benefit to the patient, tackling some of the most difficult to treat diseases.

ViaCyte is a leader in pluripotent stem cell technology and is developing novel cell replacement therapies. The initial focus is on the development of transformative therapies for patients with diabetes that require insulin. Our approach has the potential to reduce or eliminate the requirement for insulin, achieving glucose control targets with reduced risk of hypoglycemia and diabetes-related complications. ViaCyte's product candidates are based on directed differentiation of pluripotent stem cells into pancreatic islet progenitor cells, which are then implanted in durable and retrievable cell delivery devices. ViaCyte's product candidates are the first stem cell-derived therapies to be tested in clinical trials for type 1 diabetes.

The company's proprietary CyT49 pluripotent stem cell line provides a virtually unlimited supply of cells manufactured under quality-controlled conditions and hold the potential to generate any cell type present in the body through sequential steps of specialization. In collaboration with CRISPR Therapeutics, a leader in gene-editing technologies, ViaCyte is developing immune-evasive stem cell lines from its CyT49 cell line. These immune-evasive stem cell lines are being used to develop cell therapy for all patients with insulin-requiring diabetes, type 1 and type 2. However, an immune evasive pluripotent stem cell line opens up many other potential applications.

Immune-evasive cells hold the potential to unlock the true therapeutic capability of cell therapy as it would remove the burdens of immune suppression or other approaches for avoiding rejection by the host. With an immune-evasive pluripotent stem cell line and deep expertise in stem cell differentiation and clinical experience in cell therapy, ViaCyte is leading the creation and delivery of next generation cell therapies that have the potential to treat or even cure diseases that affect millions of patients around the world."

— Paul Laikind, President & CEO, ViaCyte

A key feature of the Voyager Therapeutics pipeline is that, in our lead programs for Parkinson's disease and Huntington's disease, we're leveraging a targeted surgical delivery of our gene therapies to very precise regions of the brain. We believe that this intraparenchymal approach has the important advantage of potentially bypassing certain historical and present challenges of systemically-delivered AAV gene therapies. We also continue to invest in the discovery of novel capsids specifically engineered to enhance blood-brain-barrier penetrance. These efforts may significantly broaden our ability to develop gene therapies that deliver a wide variety of payloads to specific regions, cells and genetic targets in the CNS.

— Andre Turenne, President & CEO, Voyager Therapeutics

"Over the course of the past decade, REGENXBIO's mission has remained clear: to improve lives through the curative potential of gene therapy based on our proprietary NAV® Technology Platform. We believe single administration gene therapy treatments can significantly alter the course of disease in many patient populations, including large populations of patients with ophthalmologic diseases.

We are developing our lead product candidate, RGX-314, as a novel, one-time treatment for patients with wet AMD and diabetic retinopathy using our NAV AAV8 vector, to deliver a gene encoding an anti-VEGF antibody fragment. Our Phase I/IIa trial of RGX-314 delivered subretinally for the treatment of wet AMD has yielded encouraging results across 5 dose cohorts, demonstrating significant long-term reduction of anti-VEGF treatment burden while maintaining or improving vision and retinal thickness. Later this year, we plan to initiate a pivotal RGX-314 program for wet AMD using the same subretinal route of administration, as well as Phase II trials for the treatment of wet AMD and diabetic retinopathy via suprachoroidal delivery.

If approved, our gene therapy has the potential to treat total or partial vision loss for millions of patients and reduce treatment burden for patients with these diseases. We look forward to continued development of gene therapy treatments for broader patient populations across the globe."

— Curran Simpson, SVP of Product Development & Chief Technology Officer, REGENXBIO

"I believe cell-based therapies are going to become an increasingly important player in the treatment of chronic pain conditions. Their potential to offer pain physicians a novel therapeutic strategy for patients that no longer involves a prescription to opioids or costly surgery requiring months of rehabilitation, is immense. And as a result, it is incumbent upon us in the industry to continue our efforts to validate the potential benefit of these technologies in clinical use.

At DiscGenics, we've developed a novel allogeneic cell therapy, known as IDCT, which is derived from intervertebral disc tissue to treat diseases of the disc. Our first target indication is chronic low back pain caused by degenerative disc disease, which affects approximately 5% of the global population each year. Current treatment options attempt to offer temporary pain relief; however, none of these options address the root cause of the condition: the degenerated disc. With opioid addiction at an all-time high, a non-surgical regenerative therapy that disrupts the way chronic low back pain is treated is greatly needed. Preclinical animal studies have shown that IDCT has the ability to reduce inflammation and regenerate new disc tissue to restore disc height in painful, degenerated discs. If IDCT demonstrates similar results in humans, which DiscGenics is currently evaluating through regulator-allowed clinical trials in both the U.S. and Japan, the outcome could be reduced pain and disability."

— Flagg Flanagan, Chairman & CEO, DiscGenics

Commentary: Advances in Genome Editing

Genome Editing Clinical Milestones

- There are 31 ongoing Phase 1 gene editing trials worldwide
- CRISPR joined ZFNs and TALENS in the clinic
    - First patients treated in trials to treat beta thalassemia, sickle cell (Vertex/CRISPR)
    - First patient treated in trial of CRISPR-edited TCR for sarcoma (Tmunity/PICI/Penn Medicine)
    - Evidence of successful in vivo editing in Phase 1/ 2 Study (Sangamo)
    - First *in vivo* CRISPR patient treated in March 2020
- Allogene, Cellectis, and Precision entered the clinic with gene-edited allogeneic CAR-Ts

"Precision BioSciences is excited to be one of the first companies to move gene-edited therapies into the clinic, with a gene-edited allogeneic CAR T trial actively treating patients and several *in vivo* gene therapies in our pipeline. We expect the field to make substantial advances in the next few years as more novel therapies that are enabled by genome editing enter the clinic, demonstrate activity in patients, and potentially improve upon existing treatment options. We believe this clinical validation will further demonstrate the potential of novel cell and gene therapies, including delivering one-time, truly permanent cures for patients in need."

— Nicholas Riddle, VP, Financial Strategy & Investor Relations, Precision BioSciences

"Intellia Therapeutics' full-spectrum approach is driving Intellia's diversified CRISPR/Cas9 *in vivo* and ex vivo pipelines as we enter a new era of medicine where genome editing is here to stay.

Intellia aims to improve the standard of care for patients who may only have chronic treatment options available. Intellia's lipid nanoparticle (LNP)-based CRISPR/Cas9 delivery system could have the ability to address genetic diseases with a single course of treatment, while its CRISPR-enabled engineering cell therapy approach has the potential to be more precise, potent and persistent compared to current engineered cell therapy approaches. In 2020, we expect our first in vivo systemically delivered CRISPR therapy to enter the clinic."

— Jennifer Smoter, SVP, External Affairs and Communications, Intellia Therapeutics

"It is truly an exciting time in the field of cell therapies and genetic medicines. 2019 was a pivotal year for CRISPR Therapeutics, as well as for the field of gene editing, as we and our partners, Vertex Pharmaceuticals, reported the first clinical results from two patients who were treated with CTX001, our CRISPR-Cas9 based investigational therapy targeted towards severe hemoglobinopathies. The preliminary data support our belief in the potential for CRISPR-Cas9 based therapies to have transformative benefit for patients suffering from beta thalassemia and sickle cell disease following a one-time intervention. It also underscores the rapid progression of the CRISPR technology from the discovery stage to the clinic, at a speed that is rarely seen in our industry. In parallel, we have initiated clinical trials in various oncology indications with CRISPR-engineered allogeneic cell therapies and expect to have preliminary data in 2020.

We believe that this is just the beginning for engineered cell therapies and genetic medicines. Over the next 10 years, we expect engineered cell and gene therapies to bring cures to several serious diseases, and fundamentally change the business model of the biopharma industry globally."

— Samarth Kulkarni, CEO, CRISPR Therapeutics

"In 2019, we were pleased with Sangamo's achievement of demonstrating the first evidence of in vivo genome editing and learned a great deal about delivery of our zinc finger nucleases (ZFNs) which will be instrumental to designing future *in vivo* programs and reagents. We published two important papers in Nature family journals describing new ZFN architectures enabling high-precision genome editing and strategies for optimizing the specificity of ZFNs while completely preserving efficiency. There were also preliminary clinical data readouts from our own and other ex vivo gene-edited cell therapies, and we look forward to seeing how the data mature as further patients are enrolled. Lastly, I was encouraged by the industry's focus on bioethical use of genomic medicine, as it is critical that patient safety and well-being are our top priorities.

In 2020 and beyond, I expect many more gene editing trials with different modalities to enter the clinic, and I anticipate that delivery will be addressed and solved. I also believe that gene editing trials will continue to be in rare diseases, and that over time genomic medicine will expand to larger patient populations. Further, I hope that discussions around bioethics in genomic medicines will continue to occur between our industry colleagues, the medical community, academics, and advocates, as we continue to define the ethical framework for this new frontier in medicine."

— Sandy Macrae, President and CEO, Sangamo Therapeutics

"The gene editing field has incredible potential to create durable medicines for people living with serious diseases. As therapeutic applications of CRISPR gene editing continue to mature, the insights and capabilities of early applications will lend themselves in unlocking and enabling additional therapeutic advances. Our mission is to translate the power and potential of CRISPR gene editing into a broad class of medicines that can transform lives. We are excited to leverage the unique advantages of our own gene editing platform to unlock the creation of medicines for previously untreatable disorders and help people living with serious diseases."

— Tim Hunt, Chief Corporate Affairs Officer, Editas Medicine

2019 Approvals

The following regenerative medicine products received regulatory approval in 2019:

bluebird bio received approval from the EMA for their gene therapy **Zynteglo** for the treatment of transfusion-dependent beta thalassemia in patients 12 years of age or older who do not have the β0/β0 genotype – June 3

AveXis, a Novartis company, received approval from the US FDA for their gene therapy **Zolgensma** for the treatment of spinal muscular atrophy in patients under two years of age – May 24

Novartis's CAR-T therapy **Kymriah** received approval from the Japanese Ministry of Health, Labor, and Welfare (MHLW) for the treatment of adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and for the treatment of pediatric and young adult patients with R/R B-cell acute lymphoblastic leukemia (ALL) – March 26

AnGes's nonviral gene therapy **Collategene** was approved by the Japanese MHLW for the treatment of critical limb ischemia – February 21

Kite Pharma, a Gilead company, received approval from Health Canada for their CAR-T therapy **Yescarta** for the treatment of adult patients with relapsed or refractory large B-cell lymphoma – February 19

Spinal muscular atrophy (SMA) is a rare genetic disease caused by a mutation in the survival motor neuron 1 (*SMN1*) gene. SMA affects one in every 10,000 babies born each year and is the leading cause of genetic infant death in the U.S. Friday, May 24th, 2019 marked a historic milestone for the SMA community when the U.S. FDA approved AveXis' transformative gene therapy, Zolgensma® (onasemnogene abeparvovec-xioi), for children less than two years of age with SMA. Zolgensma delivers a healthy copy of the SMN1 gene, targeting the underlying cause of SMA and halting disease progression.

AveXis has seen a positive response from the health care community, including physicians, parents of children with SMA, payers and hospitals. In 2019, approximately 200 patients were treated commercially with Zolgensma. AveXis has offered all payers pay-over-time options via a third party and outcomes-based agreements up to 5 years to support the company's belief in the long-term value of Zolgensma. In January 2020, the company reported a ~99% final approval rate for on-label patients, and 97% of commercial lives and >50% of public lives are currently covered. With over 1 million square feet in manufacturing capacity, they plan to expand gene therapy manufacturing capabilities with new sites in Colorado and North Carolina operational in 2020 and expected to be licensed in 2021.

AveXis remains committed to advancing the science behind Zolgensma to transform SMA, as well as other rare genetic diseases. They are anticipating regulatory decisions in Europe and Japan in the first half of this year for Zolgensma (AVXS-101), and have plans to develop other novel treatments for rare neurological diseases, including Rett syndrome, a genetic form of amyotrophic lateral sclerosis caused by mutations in the superoxide dismutase 1 (*SOD1*) gene, and Friedreich's ataxia. For additional information, including prescribing information and boxed warning, please visit [redacted] or www.zolgensma.com.

— Dave Lennon
President, AveXis

In June, the European Commission granted conditional marketing approval of LentiGlobin® for transfusion dependent beta thalassemia (TDT), the first gene therapy for TDT, and the first approval for a product based on the technology of lentiviral vector transduced hematopoietic stem cells. This milestone represents the dedication and commitment of scientists, clinical investigators, healthcare providers, patients and their families, and our employees, who all helped to advance this treatment from concept to approval.

Like many rare genetic diseases, the impact of TDT on the lives of patients and their families is often unappreciated beyond those living with the disease or caring for those affected.

TDT is a severe, and potentially lethal disease caused by mutations in the β-globin gene that result in reduced or absent hemoglobin. In order to survive, people living with TDT depend on frequent, lifelong blood transfusions. These transfusions carry the risk of progressive multi-organ damage due to unavoidable iron overload.

Marketed as ZYNTEGLO® (autologous CD34+ cells encoding βA-T87Q-globin gene)* in the EU, LentiGlobin for TDT is a one-time gene therapy that addresses the underlying genetic cause of TDT and offers patients 12 years and older who do not have a β0/β0 genotype the potential to become transfusion independent, which, once achieved, is expected to be lifelong — an outcome that was previously possible only with allogeneic hematopoietic

In clinical studies non-serious adverse events (AE) attributed to ZYNTEGLO were hot flush, dyspnoea, abdominal pain, pain in extremities, thrombocytopenia, leukopenia, neutropenia and non-cardiac chest pain. One serious adverse event (SAE) of thrombocytopenia was considered possibly related to ZYNTEGLO. Additional AEs observed in clinical studies were consistent with the known side effects of HSC collection and bone marrow ablation with busulfan, including SAEs of veno-occlusive disease.

This approval represents another significant milestone in the rapidly advancing field of gene therapy, which has moved beyond an investigational approach to emerge as an expanding pillar of modern medicine with recent approvals across numerous cell and vector platforms designed to treat a range of devastating diseases. The growing body of data and clinical experience serve as a foundation to extend existing gene therapy platforms
to address new diseases, and to catalyze the emergence of new technologies with the potential to bring transformational therapies to even more patients.

bluebird bio is committed to continuing our pioneering work to bring new gene therapies that deliver value to patients, caregivers, and the health care system. We are proud of our contributions to advance the science of gene therapy, and the potential of what is possible for patients.

— David Davidson
Chief Medical Officer, bluebird bio

*LentiGlobin for TDT received conditional approval in the EU, it is not approved in other markets.

Anticipated Near-Term Approvals

Several regenerative medicine developers have recently filed for regulatory approval of their product candidates, with the potential for approval in 2020:

UNITED STATES

BioMarin: ValRox
Gene therapy, hemophilia A

bluebird bio: Zynteglo
Gene therapy, beta thalassemia

Bristol-Myers Squibb: liso-cel
CAR-T therapy, r/r large B cell lymphoma

Enzyvant Tx: RVT-802
Tissue engineering, pediatric congenital athymia

FerGene: nadoferagene firadenovec
Gene therapy, bladder cancer

Kite / Gilead: KTE-X19
CAR-T therapy, mantle cell lymphoma

Mesoblast: Ryoncil
Cell therapy, graft vs. host disease

EUROPEAN UNION

AveXis / Novartis: Zolgensma
Gene therapy, spinal muscular atrophy

BioMarin: ValRox
Gene therapy, hemophilia A

Kite / Gilead: KTE-X19
CAR-T therapy, mantle cell lymphoma

Orchard Tx: OTL-200
Gene therapy, metachromatic leukodystrophy

PTC Tx: GT-AADC
Gene therapy, AADC deficiency

JAPAN

TCR Pharma / Mesoblast: TEMCELL
Cell therapy, epidermolysis bullosa

AveXis / Novartis: Zolgensma
Gene therapy, spinal muscular atrophy

List compiled from publicly available information

Anticipated Near-Term Filings

Companies that have announced they expect to file for approval in 2020 include:

UNITED STATES

Atara Bio: tab-cel
Cell therapy, EBV-associated post-transplant lymphoproliferative disease

Audentes
Gene therapy, X-linked myotubular myopathy

Bluebird / BMS: ide-cel
CAR-T therapy, multiple myeloma

Humacyte: human acellular vessel
Tissue engineering, vascular access for hemodialysis

Iovance: Lifleucel
Cell therapy, solid tumors

Iovance: LN-145
Cell therapy, solid tumors

Malinkrodt: Stratagraft
Tissue engineering, severe burns

UNITED STATES *continued*

Orchard Tx: OTL-101
Gene therapy, ADA-SCID

Orchard Tx: OTL-200
Gene therapy, metachromatic leukodystrophy

PTC Tx: GT-AADC
Gene therapy, AADC deficiency

Poseida Tx: P-BMCA-101
CAR-T therapy, multiple myeloma

EUROPEAN UNION

GenSight Bio: GS010
Gene therapy, Leber hereditary optic neuropathy

List compiled from publicly available information.

Expedited Approval Pathways

The following products received RMAT, PRIME, and/or SAKIGAKE designation in 2019:

RMAT*

Adaptimmune: ADP-A2M4
Cell therapy, synovial sarcoma
(December 3)

CARsgen: CT053
CAR-T therapy, r/r multiple myeloma
(October 28)

SanBio: SB623
Cell therapy, traumatic brain injury
(September 19)

Magenta Tx: MGTA-456
Cell therapy, multiple inherited metabolic disorders
(September 4)

Mustang Bio: MB-107
Gene therapy, XSCID
(August 12)

Orchard Tx: OTL-103
Gene therapy, Wiskott-Aldrich syndrome
(July 29)

Sangamo Tx: SB-525
Gene therapy, hemophilia A
(July 5)

Krystal Bio: KB-103
Gene therapy, dystrophic epidermolysis bullosa
(June 24)

AlloVir: Viralym-M
Cell therapy, hemorrhagic cystitis caused by BK virus following HSCT
(June 11)

Caste Creek Pharma: FCX-007
Gene therapy, recessive dystrophic epidermolysis bullosa
(May 29)

ExCellThera: ECT-001
Cell therapy, hematological malignancies
(April 23)

PRIME

Abeona Tx: ABO-102
Gene therapy, MPS IIIA
(December 12)

Rocket Pharma: RP-L102
Gene therapy, Fanconi anemia
(December 12)

Bristol-Myers Squibb: JCAR125
CAR-T therapy, r/r multiple myeloma
(November 14)

Bayer: BAY2599023
Gene therapy, hemophilia A
(October 17)

Miltenyi Biotec: MB-CAR2019.1
CAR-T therapy, diffuse large B cell lymphoma
(October 17)

CARsgen: CT053
CAR-T therapy, r/r multiple myeloma
(September 23)

Atara Bio: tab-cel
EBV-associated post-transplant lymphoproliferative disease
(May 29)

Janssen: JNJ-68284528
CAR-T therapy, multiple myeloma
(April 4)

Krystal Bio: KB-103
Gene therapy, dystrophic epidermolysis bullosa
(March 28)

Freeline Tx: FLT180a
Gene therapy, hemophilia B
(February 28)

SAKIGAKE

SanBio: SB623
Cell therapy, traumatic brain injury
(April 8)

*16 products received RMAT designation in 2019; only the 11 that have announced publicly are included here.

Outlook for Regenerative Medicine in 2020

Clinical Data Readouts

The regenerative medicine clinical pipeline is robust, with several ongoing late-stage trials. In 2020, we expect a number of high-profile data readouts from these late stage trials.

Hospital Exemption

ARM expects to participate in additional dialogue with stakeholders on safety and efficacy for point-of-care administration of cell and gene therapies, focusing particularly on appropriate implementation of the hospital exemption across European member states.

Product Approvals

There are several products poised for approval in the US, EU, and Japan in 2020. In particular, the number of approved gene therapies on the market is likely to double in the next one to two years.

Stem Cell Clinics

The FDA is expected to engage in additional enforcement activities against clinics advertising unapproved stem cell therapies, as the period of enforcement discretion comes to end in November 2020.

Sector Financings

2019 was the second strongest year for regenerative medicine financings on record. In 2020, the demand for financings will likely continue to be strong. While the IPO market may be constrained by the US election cycle, overall the indications are for another robust year for financings in the sector.

Drug Pricing

The drug pricing conversation in the US will translate into an increased emphasis on value for durable cell and gene therapies. Lawmakers will promote value-based payment (VBP) models through provisions such as Section 210 in the Senate Finance Committee's drug pricing bill, which would allow state Medicaid program to enter into VBP agreements for gene therapies for rare diseases.

Scientific Advances

There has been significant research focused on improving cell and gene therapy manufacturing and delivery in 2019, which will continue into 2020. Therapeutic developers will continue to explore strategies to combat immunogenicity and to advance allogeneic therapies.

Positive Regulatory Environment

The FDA, EMA, and other regulatory bodies will continue to engage with stakeholders to promote a positive regulatory environment for cell and gene therapies. Additional PRIME and RMAT designations are expected.

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Alliance *for* Regenerative Medicine

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