Cell & Gene Therapy – How We Successfully Enable Our Future

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What is Regenerative Medicine?

Regenerative medicine and advanced therapies include gene therapies, cell therapies, and tissue-engineered products intended to augment, repair, replace, or regenerate organs, tissues, cells, genes, and metabolic processes in the body. These therapies aim to alter the current practice of medicine by treating the root causes of disease and disorders.

Regenerative medicines are now delivering benefits for patients, with further regulatory approvals for life changing and curative treatments expected soon.
## Regenerative Medicine Technologies

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Gene Therapy</strong></td>
<td>Gene Therapy seeks to modify or introduce genes into a patient’s body with the goal of durably treating, preventing, or potentially even curing disease, including several types of cancer, viral diseases, and inherited disorders.</td>
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<tr>
<td><strong>Genome Editing</strong></td>
<td>Genome Editing is a technique by which DNA is inserted, replaced, removed, or modified at particular locations in the human genome for therapeutic benefit in order to treat cancer, rare inherited disorders, HIV, or other diseases.</td>
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<tr>
<td><strong>Cell Therapy</strong></td>
<td>Cell Therapy is the administration of viable, often purified cells into a patient’s body to grow, replace, or repair damaged tissue for the treatment of a disease. A variety of different types of cells can be used in cell therapy.</td>
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<tr>
<td><strong>Tissue Engineering</strong></td>
<td>Tissue Engineering seeks to restore, maintain, improve, or replace damaged tissues and organs through the combination of scaffolds, cells, and/or biologically active molecules.</td>
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</table>

By ARM’s standards, the following therapies are not considered ATMPs: Molecular medicines, including mRNA, RNAi, siRNA, and diagnostics-based products.
Global Regenerative Medicine Sector
Current Global Sector Landscape

953+ Regenerative Medicine Companies Worldwide, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers

Europe & Israel 233
Asia 164
North America 521
South America 13
Africa 1
Oceania 21

Source data provided by: informa
Regenerative Medicine Clinical Trials by Phase

1,071 RM/AT Trials Currently Ongoing
- Phase 3: 96
- Phase 2: 609
- Phase 1: 366

- 100% increase in Phase 3 trials since Q1 2015
- 111% increase in Phase 2 trials since Q1 2015
- 144% increase in Phase 1 trials since Q1 2015

Source data provided by: informa
Currently Ongoing RM/AT Clinical Trials by Therapeutic Area

- **62% (663)** 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.

- **5% (57)** are in **musculoskeletal disorders**, including muscular dystrophies, spinal muscular atrophy, osteoarthritis, degenerative disc disease, bone and cartilage defects, and others.

- **5% (55)** are in **central nervous system disorders**, including multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, traumatic brain injury, ALS, and others.

Source data provided by: informa
Total Financings by Technology, by Year

YTD 2019 financings calculated as of September 20, 2019

Source data provided by: informa
Total Financings by Type, by Year

YTD 2019 financings calculated as of September 20, 2019

Corporate Partnerships (Upfront Payments Only)
- YTD 2019: $1,148
- 2018: $1,088
- 2017: $1,563

Private Placements / PIPES
- YTD 2019: $731
- 2018: $689
- 2017: $1,237

Follow On / Secondary Public Offering
- YTD 2019: $1,890
- 2018: $3,995
- 2017: $4,715

IPO
- YTD 2019: $387
- 2018: $1,927
- 2017: $254

Venture Capital
- YTD 2019: $1,451
- 2018: $2,913
- 2017: $1,451

Source data provided by: informa
Total M&A Transactions Values, By Year
YTD 2019 financings calculated as of September 20, 2019

*Mergers & Acquisitions*

$-$ $2,000 $4,000 $6,000 $8,000 $10,000 $12,000 $14,000 $16,000 $18,000 $20,000

- $5,261
- $12,720
- $18,944

*YTD 2019
- 2018
- 2017

*Does not include Roche’s planned $4.3B acquisition of Spark Therapeutics (expected to close by EOY 2019).*

Source data provided by: informa
Cell & Gene Therapy in Maryland
Regenerative medicine companies active in Maryland, including 28 therapeutic developers:

- Columbia
- Sparks
- Eldersburg
- Baltimore
- Halethorpe
- Hanover
- Beltsville
- Walkersville
- Frederick
- Germantown
- Gaithersburg
- Rockville
- Bethesda
- Silver Spring

Gene Therapy: 10
Cell Therapy: 18
Tissue Engineering: 4
Tool, technology, & service providers: 9+
Select Financings & Business News

- Neuralstem* raises $7.5M in follow-on public offering – July 31, 2019
- RoosterBio* raises $22M in Series B financing – September 10, 2019
- REGENXBIO* and Clearside Biomedical sign agreement worth up to $136M for the use of Clearside’s SCS Microinjector for the delivery of RGX-314 in the treatment of AMD, diabetic retinopathy, and other ophthalmologic diseases – September 4, 2019
- Northwest Biotherapeutics signs $2M upfront manufacturing services agreement with Cognate Biosciences* – May 28, 2019
- MaxCyte* raises £10M in placement of stock – February 5, 2019
- Autolus announced $28M investment in new Rockville headquarters, expected to create 170 jobs – January 14, 2019
- Intrexon / Precigen* and Merck sign $150M upfront agreement for the development of Precigen’s CAR-T programs – December 20, 2018
- REGENXBIO* enters into a $20M upfront agreement with Abeona Therapeutics to develop therapies for MPS IIIA, MPS IIIB, CLN1 disease, and CLN3 disease – November 4, 2018
- Precigen* and ZIOPHARM Oncology sign agreement worth up to $311M for the development of therapies for cancer – October 5, 2018
- Collplant and United Therapeutics* enter into agreement worth up to $24M for an additional 3 tissue engineering programs – October 22, 2018
- REGENXBIO* and AveXis sign $80M upfront agreement for the development of gene therapies for spinal muscular atrophy – January 8, 2018
  - REGENXBIO* receives $100M accelerated license payment due to Novartis acquisition of AveXis – June 11, 2018
108 RM/AT Clinical Trials Ongoing in Maryland

**By Phase**
- **Ph 3, 23**
- **Ph 1, 24**
- **Ph 2, 30**
- **Ph 1/2, 31**

**By Tech Type**
- **Gene therapy, 37**
- **Cell therapy, 15**
- **Tissue engineering, 7**
- **Gene-modified cell therapy, 49**
108 RM/AT Clinical Trials Ongoing in Maryland

- Oncology: 73
- Ophthalmology: 6
- Musculoskeletal: 6
- Immunology and Inflammation: 5
- Cardiovascular: 4
- Central Nervous System: 3
- Endocrine, Metabolic & Genetic Disorders: 2
- Hematology: 2
- Genitourinary Disorders: 2
- Gastroenterology: 2
- Infectious Diseases: 1
- Geriatric Diseases: 1
- Ear Diseases: 1
Clinical Trial Sponsors
With Active Trials in Maryland

- Adaptimmune
- Aduro Biotech, Inc.
- Advantagene, Inc.
- Advaxis, Inc.
- Amgen
- Anchiano Therapeutics Israel Ltd.
- Applied Genetic Technologies Corp
- Audentes Therapeutics
- AveXis, Inc.
- Axogen Corporation
- Axovant Sciences, Inc.
- Bayer
- BioCardia, Inc.
- bluebird bio
- Boston Children’s Hospital
- Bristol-Myers Squibb
- Cartesian Therapeutics
- Celgene
- Children's Research Institute
- Dendreon
- FKD Therapies
- Gamida Cell Ltd
- Genethon
- GlaxoSmithKline
- Humacyte, Inc.
- Icahn School of Medicine at Mount Sinai
- Iovance Biotherapeutics, Inc.
- Johns Hopkins University
- Juno Therapeutics, Inc.
- Kite, A Gilead Company
- Longeveron LLC
- Loyola University Medical Center (LUMC)
- MaxCyte, Inc.
- Medeor Therapeutics, Inc.
- MedImmune LLC
- MeiraGTx UK II Ltd
- Merck Sharp & Dohme Corp.
- Mesoblast
- MiMedx Group, Inc.
- National Institutes of Health (NIH)
- Neurotech Pharmaceuticals
- NightstaRx Ltd
- Novartis Pharmaceuticals
- Pluristem Ltd.
- Poseida Therapeutics, Inc.
- Regenxbio Inc.
- ReNeuron Limited
- Sotio a.s.
- Takeda
- Targovax ASA
- TCR2 Therapeutics
- Tigenix S.A.U.
- Tocagen Inc.
- Trizell Ltd
- University of California, Los Angeles
- University of Pennsylvania
- Unum Therapeutics Inc.
- VBL Therapeutics
- Vericel Corporation
- ViaCyte
- Washington University School of Medicine
Thank you!

Q&A
Current Areas of Focus
Recent ARM Successes

**RMAT Designation**
Creation of the RMAT designation to bring safe & effective therapies to market quickly

**Gene Therapy**
Inclusion of gene therapies in the RMAT designation

**RAC Reform**
NIH ended duplicative review of gene therapy trials

**Gene Editing**
Published Therapeutic Developers Statement of Principles
Market Access & Reimbursement

Drive Adoption of New Payment Models and Value-based Reimbursement

• Lobby in support of legislation in the U.S.
  • Held 90+ meetings with congressional offices during ARM Fly-In
  • Organized Congressional educational briefings on gene therapy, market access
  • *Key Provisions included in Senate Finance Committee-approved bill*

• Testified at the CMS Town Hall, filed comments, met with CMS seeking improvements in CAR-T coverage and reimbursement
  • *NTAP increased from 50% to 65%*
  • *National Coverage Decision finalized*
  • *CMS will consider CAR-T DRG for FY 2021*

• Analytical Work
  • Summer ‘19: Status of market access for ATMPs in key European countries, including barriers to and recommendations for timely patient access
  • Fall ‘19: Roadmap for Managed Care Access, w/NAMCP
  • Fall ‘19: Potential Cost Saving of Cell And Gene Therapies For The Next Decade

*ARM presents Senator Cassidy with the Legislator of the Year Award, 2019*
# Market Access Landscape

*As of September 2019*

<table>
<thead>
<tr>
<th>Country (HTA/Payer)</th>
<th>Drugs Approved</th>
<th>HTA/Payer Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>France (TC/CEESP)</td>
<td>Kymriah, Alofisel, Yescarta, Luxturna, Zalmoxis</td>
<td>Positive HTA/Payer Opinion, Reimbursed</td>
</tr>
<tr>
<td>Germany (IQWIG/G-BA)</td>
<td>Imlygic, Kymriah, Imlygic, Strimvelis, Yescarta, Luxturna</td>
<td>Positive HTA/Payer Opinion, Reimbursed</td>
</tr>
<tr>
<td>UK (NICE/SMC)</td>
<td>Holoclar, Holoclar, Imlygic, Kymriah, Strimvelis, Yescarta, Luxturna</td>
<td>Positive HTA/Payer Opinion, Reimbursed</td>
</tr>
<tr>
<td>Italy (AIFA/regional)</td>
<td>Holoclar, Holoclar, Imlygic, Kymriah, Strimvelis, Yescarta, Luxturna</td>
<td>Positive HTA/Payer Opinion, Reimbursed</td>
</tr>
<tr>
<td>U.S. (CMS &amp; FDA)</td>
<td>Imlygic, Kymriah, Luxturna, Zalmoxis, Yescarta</td>
<td>Positive HTA/Payer Opinion, Reimbursed</td>
</tr>
<tr>
<td>Canada (CADTH)</td>
<td>Kymriah</td>
<td>CADTH Assessment: Would be cost effective if price lowered</td>
</tr>
<tr>
<td>Australia (MSAC)</td>
<td>Kymriah, Yescarta, Collategene</td>
<td>Positive HTA/Payer Opinion, Reimbursed</td>
</tr>
<tr>
<td>Japan (PMDA)</td>
<td>Kymriah</td>
<td>Positive HTA/Payer Opinion, Reimbursed</td>
</tr>
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</table>

Zynteglo, which was approved in Europe in June 2019, is currently working with payers in UK, Italy, Germany, France for its initial commercial rollout in 2020.
Regular engagement with the FDA & EMA

- Topics: disease specific guidances, CMC requirements, registries, good clinical practice, trial design, European repository of regulatory requirements, GMO harmonization, ARM’s analysis of the discrepancies in US and EU regulations for ATMPs, etc.
Overcoming Manufacturing Barriers

- Member workshop on comparability in cell & gene therapy development, with USP & global regulators
- *In Vivo* publication on manufacturing challenges in cell and gene therapy in June, and co-hosted a follow-up webinar in September
- Finalizing a comprehensive framework document -- A-Gene -- covering development, manufacture, regulatory submission, and lifecycle of gene therapies
  - Expected release in early 2020
  - Content is currently being drafted for A-Cell, a similar project focusing on cell therapies

*A-Gene participants include:*
International Dialogue on Bioethics

• Elevated Industry voice in the gene editing international dialogue by releasing a Therapeutic Developers’ Statement of Principles on Human Genome Editing
  • Signed by 14 preeminent companies active in developing gene-edited therapies.
    • Audentes, bluebird bio, BlueRock, Caribou Bio, Casebia, CRISPR, Editas, Homology, Intellia, LogicBio, Precision, Sangamo, Tmunity, Pfizer
  • Asserted that the clinical use of germline gene editing is currently inappropriate
• Presented at an August 27 meeting of the WHO’s expert advisory panel on human genome editing in Geneva; Engaged with NAS gene editing panel

Biotech companies issue first declaration on human gene editing

Industry declares that it will not make DNA changes affecting future generations
Near-Term Anticipated Product Approvals
## Recently Approved Products

<table>
<thead>
<tr>
<th>Therapy Name</th>
<th>Product Developer</th>
<th>Response</th>
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</thead>
</table>
| Kymriah      | Novartis          | • 40% of patients with R/R DLBCL treated experienced a complete response  
|              |                   | • 60% of patients with R/R B-Cell ALL treated experienced a complete response |
| Yescarta     | Kite Pharma, a Gilead company | • 58% of patients with R/R B-Cell NHL treated experienced a complete response |
| LUXTURNA     | Spark Therapeutics | • 55% of patients treated showed an improvement of 2+ light levels darker after treatment |
| Zolgensma    | AveXis / Novartis | • 93% of patients SMA Type 1 treated were alive without permanent ventilation at 24 months post-treatment |
| Zynteglo     | bluebird bio      | • 75% of patients with TDT without β0/β0 genotype treated achieved transfusion independence |
Select Anticipated Near-Term Approvals (Global)

**Gene Therapy**

**Zolgensma** (AveXis / Novartis)
- Spinal muscular atrophy type 1
- Decision expected: mid 2019 (EU & Japan)

**GT-AADC** (PTC Therapeutics)
- AADC deficiency
- Expects to file: late 2019 (US)

**Zynteglo** (bluebird bio)
- Beta thalassemia
- Expects to file: 2019 (US)

**Valrox** (BioMarin)
- Hemophilia A
- Expects to file: Q4 2019 (US & EU)

**GS010** (GenSight Biologics)
- Leber hereditary optic neuropathy
- Expects to file: H2 2020 (US & EU)

**AT132** (Audentes Therapeutics)
- X-linked myotubular myopathy
- Expects to file: H2 2020 (US)

**OTL-101** (Orchard Therapeutics)
- ADA-SCID
- Expects to file: 2020 (US)

**OTL-200** (Orchard Therapeutics)
- Metachromatic leukodystrophy
- Expects to file: 2020 (US & EU)
Select Anticipated Near-Term Approvals (Global)

**Cell-Based Immuno-Oncology**

- **Rivo-cel** (Bellicum Pharmaceuticals)
  - HSCT to treat blood cancers
  - Expects to file: EOY 2019 (EU)

- **tab-cel** (Atara Biotherapies)
  - EBV-PTLD
  - Expects to file: 2H 2019 (US)

- **liso-cel** (Celgene)
  - Diffuse large B-cell lymphoma (DLBCL)
  - Expects to file: Q4 2019 (US)

- **ide-cel** (bluebird bio / Celgene)
  - Multiple myeloma
  - Expects to file: 1H 2020 (US)

- **ATIR101** (Kiadis Pharma)
  - HSCT to treat blood cancers
  - Decision expected: 1H 2020 (EU)

- **P-BCMA-101** (Poseida Therapeutics)
  - Multiple myeloma
  - Expects to file: 2020 (US)

- **Lifileucel** (Iovance)
  - Advanced metastatic melanoma
  - Expects to file: 2020 (US)

- **LN-145** (Iovance)
  - Advanced metastatic cervical cancer
  - Expects to file: 2H 2020 (US)
Select Anticipated Near-Term Approvals (Global)

**Cell Therapy**

- **SB623** (SanBio)
  - Traumatic brain injury
  - Expects to file: January 2020 (Japan)

- **Remestemcel-L** (Mesoblast)
  - Acute graft versus host disease
  - Decision expected: 2020 (US)

- **TEMCELL** (Mesoblast / JCR Pharma)
  - Epidermolysis bullosa
  - Decision expected: 2020 (Japan)

**Tissue-Based**

- **RVT-802** (Enzyvant Therapeutics)
  - Complete DiGeorge anomaly
  - Decision expected: 2019 (US)

- **Humacyl** (Humacyte)
  - End stage renal disease
  - Expects to file: 2020 (US)

- **Stratagraft** (Mallinckrodt)
  - Deep partial thickness burns
  - Expects to file: 2020 (US)
Select Corporate Partnerships & Public Financings YTD 2019

Corporate Partnerships: (Upfront Payments)
- Genentech/Roche signs $300M upfront agreement with Adaptive Biotechnologies – January 4
- Vertex signs $175M upfront agreement with CRISPR Tx – June 6
- Neurocrine Bio and Voyager Tx sign $115M upfront agreement – January 29
- Mesoblast signs $150M upfront agreement with Grünenthal – September 10
- Janssen signs $100M upfront agreement with MeiraGTx – January 31
- Astellas signs $80M upfront agreement with Frequency Therapeutics – July 17

Private Placements & Venture Financings:
- Century Therapeutics launches with $250M – July 1, 2019
- Maze Tx raises $191M in venture funding – February 28
- Poseida raises $142M in Series C – April 22
- Beam Tx secures $135M in Series A – March 6
- Achilles Tx raises $121 in Series B – September 3
- AlloVir raises $120M in Series B – May 22
- Passage Bio raises $115.5M in Series A – February 15
- Nkarta raises $114M in Series B – September 4
- Passage Bio raises $110M in Series B – September 4
- Talaris Tx raises $100M in Series A – April 18
- Juvenescence raises $100M in Series B – August 19

Public Offerings: (IPOs & Follow-Ons)
- uniQure raises $225M in follow-on offering – September 4
- Fate Tx raises $173M in follow-on offering – September 18
- Atara raises $150M in follow-on offering – July 23
- Sangamo raises $145M in follow-on offering – April 8
- Precision Bio raises $145M in IPO – April 1
- Homology raises $144M in follow-on offering – April 12
- AVROBIO raises $138M in follow-on offering – July 19
- Orchard Tx raises $128M in follow-on offering – June 3
- Prevail Tx raises $125M in IPO – June 24
- Autolus raises $115.9M in follow-on offering – April 15
- Krystal Bio raises $115M in follow-on offering – June 24
This presentation will be available on our website and shared via Twitter at @alliancemrm

Visit www.alliancemrm.org to access additional resources, including:

- Quarterly sector data reports
- 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
Thank You!