Agenda

- ARM Overview
- Global Sector Overview
- Clinical Progress
- Anticipated Clinical Data Events
- Sector Financings
- Public Policy Overview
About ARM

• **International advocacy organization**
  • Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
  • Cell and gene therapy, tissue engineering

• **350+ members**
  • Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
  • Across 25 countries

• **Priorities:**
  • Clear, predictable, and harmonized **regulatory** pathways
  • Enabling market access and value-based **reimbursement** policies
  • Addressing industrialization and **manufacturing** hurdles
  • Compile sector data, **educate** media and other stakeholders
Current Global Sector Landscape

987+ Regenerative Medicine Companies Worldwide

534 North America

237 Europe & Israel

180 Asia

13 South America

22 Oceania

1 Africa

Australia, New Zealand, Marshall Islands
2019 has been a significant year of growth for the regenerative medicine sector

- 24 RM Products Granted RMAT, PRIME, and/or SAKIGAKE Designations in 2019
- 1,066 Ongoing RM/AT Clinical Trials
- $9.8B Raised in Global Financings in 2019
# Patient Impact of Recently Approved Products

<table>
<thead>
<tr>
<th>Therapy Name</th>
<th>Product Developer</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zynteglo</td>
<td>bluebird bio</td>
<td>• 75% of patients with TDT without β0/β0 genotype treated achieved transfusion independence</td>
</tr>
<tr>
<td>Zolgensma</td>
<td>AveXis, a Novartis company</td>
<td>• 93% of SMA Type 1 patients treated were alive without permanent ventilation at 24 months post-treatment</td>
</tr>
<tr>
<td>LUXTURNA</td>
<td>Spark Therapeutics</td>
<td>• 93% of patients treated showed an improvement of at least 1 light level from baseline</td>
</tr>
<tr>
<td>Yescarta</td>
<td>Kite Pharma, a Gilead company</td>
<td>• 58% of patients with R/R B-Cell NHL treated experienced a complete response</td>
</tr>
</tbody>
</table>
| Kymriah      | Novartis          | • 40% of patients with R/R DLBCL treated experienced a complete response  
• 82% of patients with R/R B-Cell ALL treated experienced complete remission or complete remission with incomplete hematologic recovery |

- 60,000+ patients to be enrolled in RM clinical trials  
- 500,000+ patients treated with cell and gene therapies by 2030 in the US alone*

*MIT NEWDIGS estimate
Select Anticipated Approvals in 2020

**Gene Therapy**

**Zolgensma** (AveXis / Novartis)
- Spinal muscular atrophy type 1
- Filed for approval in EU and Japan mid-2019

**ValRox** (BioMarin)
- Severe hemophilia A
- Filed for approval in US and EU in December 2019

**OTL-200** (Orchard Therapeutics)
- Metachromatic leukodystrophy
- Filed for approval in the EU in December 2019

**GT-AADC** (PTC Therapeutics)
- AADC deficiency
- Filed for approval in EU in January 2020

**Zynteglo** (bluebird bio)
- Beta thalassemia
- Filed for approval in US in January 2020

**Cell Therapy**

**Remestemcel-L** (Mesoblast)
- Acute graft versus host disease
- Initiated rolling BLA in US in May 2019

**TEMCELL** (Mesoblast / JCR Pharma)
- Epidermolysis bullosa
- Filed for market approval for additional indication in Japan in March 2019

**Cell-Based Immuno-Oncology**

**liso-cel** (Bristol-Myers Squibb)
- Relapsed or refractory large B cell lymphoma
- Filed for approval in the US in December 2019

**KTE-X19** (Kite Pharma / Gilead)
- Relapsed or refractory mantle cell lymphoma
- Filed for approval in the US in December 2019

**Tissue Engineering**

**RVT-802** (Enzyvant Therapeutics)
- Pediatric Congenital Athymia
- US filing accepted for review in June 2019

**Expecting to file in 2020:**
- Atara Bio – tab-cel
- Audentes Tx – AT132
- bluebird bio / BMS – ide-cel
- GenSight Bio – GS010
- Humacyte – Human Acellular Vessel
- Iovance – LN-145, lifileucel
- Mallinkrodt – Stratagraft
- Orchard – OTL-101, OTL-200 (US)
- PTC Tx – GT-AADC (US)
- Poseida – P-BMCA-101

**GT-AADC** (PTC Therapeutics)
- AADC deficiency
- Filed for approval in EU in January 2020

**Zynteglo** (bluebird bio)
- Beta thalassemia
- Filed for approval in US in January 2020
The Clinical Landscape for Regenerative Medicine in the US

Phase 1: 210
- Gene Therapy: 76
- Gene-Modified Cell Therapy: 113
- Cell Therapy: 17
- Tissue Engineering: 4

Phase 2: 300
- Gene Therapy: 138
- Gene-Modified Cell Therapy: 101
- Cell Therapy: 54
- Tissue Engineering: 7

Phase 3: 62
- Gene Therapy: 27
- Gene-Modified Cell Therapy: 13
- Cell Therapy: 12
- Tissue Engineering: 10

572 Ongoing Regen Med Clinical Trials with US trial sites

Approximately ½ of ongoing regenerative medicine trials worldwide have a clinical trial site in the US.
The Clinical Landscape for Regenerative Medicine in the US

**Phase 1: 210**
- Gene Therapy: 76
- Gene-Modified Cell Therapy: 113
- Cell Therapy: 17
- Tissue Engineering: 4

**Phase 2: 300**
- Gene Therapy: 138
- Gene-Modified Cell Therapy: 101
- Cell Therapy: 54
- Tissue Engineering: 7

**Phase 3: 62**
- Gene Therapy: 27
- Gene-Modified Cell Therapy: 13
- Cell Therapy: 12
- Tissue Engineering: 10

54% of Phase 1 Trials are in gene-modified cell therapies
Clinical Trials Across Diverse Indications

Global Clinical Trials

- Oncology: 657
- Musculoskeletal: 60
- Central Nervous System: 57
- Endocrine, Metabolic and Genetic Disorders: 55
- Cardiovascular: 46
- Hematology: 35
- Ophthalmology: 33
- Immunology and Inflammation: 31
- Dermatology: 23
- Infectious Diseases: 20
- Genitourinary Disorders: 16
- Gastroenterology: 16
- Respiratory: 10
- Geriatric Diseases: 3
- Lymphatic Diseases: 2
- Ear Diseases: 1
- Surgery: 1
Increasing Clinical Activity in Larger Indications Globally

More prevalent indications indicated in purple

- **Oncology**
  - 657
- **Musculoskeletal**
  - 60
- **Central Nervous System**
  - 57
- **Endocrine, Metabolic and Genetic Disorders**
  - 55
- **Cardiovascular**
  - 46
- **Hematology**
  - 35
- **Ophthalmology**
  - 33
- **Immunology and Inflammation**
  - 31
- **Dermatology**
  - 23
- **Infectious Diseases**
  - 20
- **Genitourinary Disorders**
  - 16
- **Gastroenterology**
  - 16
- **Respiratory**
  - 10
- **Geriatric Diseases**
  - 3
- **Lymphatic Diseases**
  - 2
- **Ear Diseases**
  - 1
- **Surgery**
  - 1

- 40 ongoing clinical trials in common cardiovascular indications
- 23 trials in diabetes and related complications
- 19 trials in aging-associated neurological disorders
- 15 trials in common musculoskeletal disorders and injuries
- 10 trials in stroke and stroke recovery
Advances in Gene Therapy Delivery

Researchers drove progress in gene therapy delivery methods:

Non-viral delivery advancements:
- Japan approved Colletagene, a non-viral gene therapy to treat critical limb ischemia
- There are currently 57 ongoing gene therapy trials utilizing non-viral delivery methods

Companies are partnering to overcome challenges in gene therapy & gene-modified cell therapy manufacturing:
- Ziopharm Oncology and MD Anderson announced a new R&D agreement to expand TCR-T program
- SQZ Biotech and AskBio announced collaboration to overcome AAV immunogenicity
Expanding Manufacturing Capabilities

Numerous companies invested in in-house manufacturing capabilities:

- **Reuters**: Pfizer, Novartis lead $2 billion spending spree on gene therapy production

- **Bloomberg**: Kite Announces Plans for New State-of-the-Art Facility to Expand Cell Therapy Production Capabilities

- **Brief**: Thermo Fisher opens $90M viral vector manufacturing plant in Massachusetts
Expanding Manufacturing Capabilities

Pre-market companies invested in manufacturing early:

- Audentes announced addition of cGMP plasmid manufacturing to existing large scale AAV operations
- REGENXBIO announced new manufacturing facility, to be operational in 2021
- ElevateBio launched with $150M to provide centralized R&D and manufacturing capabilities to suite of CGT developers
- Precision BioSciences opened first in-house cGMP manufacturing facility dedicated to genome-edited allogeneic CAR-Ts in the US
Expanding Manufacturing Capabilities

CMOs were attractive acquisition targets in 2019:

- Novartis acquires CellforCure to boost CAR-T manufacturing
- Hitachi gets EU cell manufacturing facilities with deal to buy Apceth Biopharma
- Thermo Fisher to Acquire Brammer Bio for $1.7B
- Catalent acquires gene therapy specialist Paragon for $1.2bn
Financing Trends

✓ Total global financings in 2019 second highest ever for the sector
✓ Strong year for venture financing and corporate partnerships
✓ Large- and mid-cap pharma company M&A interest in cell & gene therapy
✓ European companies had a strong year for financings, on par with 2018
Total Global Financings 2019

$9.8B
Total Global Financings in 2019

$7.6B
Gene-Based Therapies

$5.1B
Cell Therapy

$442M
Tissue Engineering

*both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies – therefore, total financings does not equal the sum of each technology category

Source data provided by: informa
2019 surpassed 2015 in total global financings, making it the second highest year for financings ever

Source data provided by: informa

**M&A not included**
M&A Activity Reflects Growing Interest in Cell & Gene Therapy

Large and mid-cap pharma/bio acquisitions in the sector:

- Astellas acquires Audentes Tx for $3B*
- Roche acquires Spark Tx for $4.8B
- Vertex acquires Semma for $950M
- Biogen acquires Nightstar Tx for $877M
- Bayer acquires remaining stake in BlueRock Tx for $240M

*Not included in 2019 figure; deal closed in Q1 2020 and will be included in 2020 figures
Policy Environment
Supportive Regulatory Environment

“We anticipate that by 2020 we will be receiving more than 200 INDs per year, building upon our total of more than 800 active cell-based or directly administered gene therapy INDs currently on file with the FDA. And by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and the clinical success rates of these products.”

- FDA Commissioner Scott Gottlieb and CBER Director Peter Marks, January 2019

The FDA is actively involved in creating a positive regulatory environment for regenerative medicines and advanced therapies:

- Two CMC specific guidances for cell and gene therapies released January 2020
- Disease-specific guidances on hemophilia, rare diseases, retinal disorders, January 2020
- Gene therapy “sameness” draft guidance released January 2020
- Supporting the Future of Rare Disease Product Development Public Meeting, February 2020
Positive Market Access Developments

- **CMS National CAR-T Coverage Decision**
  - Medicare coverage for all FDA-approved products

- **FY 2020 Inpatient Prospective Payment System Rule**
  - Gathering data for potential CAR-T DRG

- **Congressional CAR-T letter to CMS**

- **U.S. Senate VBP Provision; House VBP Bill**
Sector Challenges

- **Reimbursement Models**
  - Public Payer: Regulatory/Legislative Roadblocks
  - Commercial: One-offs
  - CAR-T: Reimbursement inadequate/impact on patient access

- **FDA**
  - CGT Reviewers

- **Manufacturing**
  - Manpower
  - Scale-up
CAR-Ts

- **Current Challenges**
  - Current reimbursement inadequate
  - Add-on payment set to expire in 2020
  - Patient access

- **Crystal Ball Future**
  - More “traditional” CAR-Ts
  - Local site manufacturing
  - Off-the-shelf / allogeneic therapies
    - Cellectis, Precision, Celyad entered the clinic in 2019 with gene-edited allogeneic CAR-Ts
    - Increased preclinical activity and some clinical activity (Fate Tx) in allogeneic CAR-Ts utilizing iPSCs
  - Increasing interest in CAR-Ts outside of oncology
    - Cartesian initiated clinical trial of their CAR-T for Generalized myasthenia gravis (autoimmune disorder)
    - Sangamo has received approval from the UK to initiate a trial of their CAR-Treg product to prevent immune rejection following kidney transplant
Looking Forward: 2020+
The Outlook for 2020

**Clinical Data Readouts**
Numerous high-profile data readouts expected in 2020

**Product Approvals**
Several anticipated product approvals; gene therapies likely to double within 1-2 years

**Sector Financing**
Strong demand for financing; IPO market constrained by US elections; indications generally strong

**Gene Therapy Advances**
Continued improvements in gene therapy delivery & manufacturing

**Hospital Exemption**
Additional focus on safety & efficacy for point-of-care administration

**Stem Cell Clinics**
Additional enforcement actions to be taken against ‘rogue’ stem cell clinics

**Drug Pricing**
Moderate solution with increased emphasis on value in the RM sector

**Regulatory Environment**
Continued support for the sector, with additional RMAT / PRIME designations expected