About ARM

- **International advocacy organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world

- **300 + members**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders

- **Priorities:**
  - Clear, predictable, and harmonized regulatory pathways
  - Enabling market access and value-based reimbursement policies
  - Addressing industrialization and manufacturing hurdles
  - Conducting key stakeholder outreach, communication, and education
  - Facilitating sustainable access to capital
ARM CMC Initiatives

• Submitted 4 formal responses to CMC-related FDA regulatory guidance documents in 2018
• 20+ ARM members and other industry consortia:
  • A-Gene project – a single case study based white paper compiling expertise on the development and manufacture of gene therapy products expected in 2019.
  • A-Cell project, an analogous white paper for cell therapies.
• Hosted the second annual CMC workshop in Fall 2018 with an open forum for discussion of current CMC & QC concerns, with FDA leadership
ARM Membership
**Members in bold are publicly traded companies**

ARM Membership

Currently: 316 Total Members

32%
Average Annual Growth Rate

Membership Growth
State of the Industry

• Global Sector Overview
• Clinical Progress
• Patient Impact
• Anticipated Clinical Data Events
• Sector Financings
• Public Policy
A Quick Note -

This presentation will be available via:

- ARM’s website: www.alliancerm.org
- Twitter @alliancerm
Global Sector Overview
Current Global Sector Landscape

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

North America: 484
South America: 15
Europe & Israel: 241
Asia: 142
Africa: 1
Oceania: 23

Source data provided by: informa
**Major Therapeutic Platforms & Enabling Technologies**

- **Smart biomaterials**: biosynthetic materials, 3D printable inks, synthetic and naturally-derived scaffolds, biofunctional materials, mechanical characterization of materials, effect of biomaterial characteristics on cell differentiation.

- **Tissue substitutes**: New cell-based tissues, collagen, induced pluripotent stem cell-derived cells, tissues and organoids.

- **Advanced cells**: Modified T-cells; hematopoietic stem cells; iPSCs; mesenchymal stem cells; adult progenitor cells (neural, liver, cardiac); etc.

- **Cell-based immunotherapies**: chimeric antigen receptors (CAR) T cell therapies, T cell receptor (TCR) therapies, natural killer (NK) cell therapies, tumor infiltrating lymphocytes (TILs), marrow derived lymphocytes (MILs), gammadelta T cells, and dendritic vaccines.

- **Novel and synthetic gene delivery vehicles**: Viral vectors: retroviruses, adenoviruses, herpes simplex, vaccinia, and adeno-associated virus (AAV); non-viral vectors, including nanoparticles, nanospheres, transposons, electroporation, and others.

- **Genome editing**: meganucleases, homing endonucleases; zinc finger nucleases (ZFNs); transcription activator-like effector-based nucleases (TALEN); nucleases such as Cas9 and Cas12a that derive from the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas); homologous recombination of adeno-associated virus (AAV)-derived sequences.

- **Next-gen expression constructs**: novel capsids; innovative regulatory elements, including synthetic promoters that enable specificity, strength, and improve capacity; inducible elements to regulate gene expression temporally or in response to external stimuli: molecular kill switches to improve safety; etc.
Clinical Progress
Product Approvals in 2018

- Spark Therapeutics’ **LUXTURNA** gene therapy for biallelic RPE65-mediated inherited retinal disease received EC approval – November 23

- Avita Medical’s **RECELL** cell therapy for serious burns received FDA approval for the treatment of severe burns – September 20

- Gilead / Kite Pharma’s **Yescarta** cell therapy received approval from the European Commission for the treatment of DLBCL – August 27; approval from the European Commission to treat adult patients with r/r DLBCL and PMBCL – August 27

- MiMedx’s **Amniofix** and **EpiFix** tissue matrix allografts received approval from the Australian TGA for wound treatment – August 9; MidMex’s **EpiBurn** tissue matrix allograft received approval from the Australian TGA for the treatment of burns – August 9

- Novartis’s **Kymriah** cell therapy received FDA approval for a second indication: treatment of adult patients with r/r large B-cell lymphoma – May 1; approval from the European Commission for adult patients with r/r DLBCL and patients under the age of 25 with ALL – August 27; approval from the Australian TGA for adult patients with r/r DLBCL and patients under the age of 25 with ALL – December 18

- TiGenix’s (now Takeda’s) **Alofisel** allogeneic stem cell therapy for treatment of perianal fistulas in Crohn’s disease patients received central marketing authorization from the European Commission – March 23
Total Clinical Trials by Phase, EOY 2018

Phase I: 341
Phase II: 595
Phase III: 92

**TOTAL:**
1,028
Total Clinical Trials by Technology Type, EOY 2018

Gene Therapy
Total: 362
Phase I: 120
Phase II: 210
Phase III: 32

Gene-Modified Cell Therapy
Total: 362
Phase I: 158
Phase II: 188
Phase III: 16

Cell Therapy
Total: 263
Phase I: 53
Phase II: 177
Phase III: 33

Tissue Engineering
Total: 41
Phase I: 10
Phase II: 20
Phase III: 11

Source data provided by: informa
Clinical Trials by Therapeutic Category

- **58% (598)** 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.

- **7% (67)** are in **cardiovascular disorders**, including congestive heart failure, myocardial infarction, critical limb ischemia, heart disease, and others.

- **6% (58)** are in **musculoskeletal disorders**, including spinal muscular atrophy, osteoarthritis, muscular dystrophies, cartilage defects, and bone fractures and disorders, and others.

Source data provided by: informa
Total Targeted Enrollment of Patients in Current Regenerative Medicine Clinical Trials Worldwide

- **59,575**
- **9,533** Target Enrollment of Phase I Clinical Trials
- **29,069** Target Enrollment of Phase II Clinical Trials
- **20,973** Target Enrollment of Phase III Clinical Trials

Source data provided by: informa
Patient Impact of Regenerative Medicine

**KYMRIAH**
Estimated patient population of 400 per year in the U.S.

**R/R B-Cell ALL Response Rates:**
*Eliana Trial – January 2018*
- Objective Response Rate: 81%
- Complete Response Rate: 60%

**R/R DLBCL Response Rates:**
*Juliet Trial – June 2018*
- Objective Response Rate: 52%
- Complete Response Rate: 40%

**LUXTURNA**
Estimated patient population: 1,000 to 3,000 patients in the U.S.

**Efficacy:**
- 55% of clinical trial participants showed an improvement of at least 2 light levels darker after treatment
- 65% of clinical trial participants were able to navigate through a mobility test course equivalent to a moonless summer night

**YESCARTA**
Estimated patient population of 5,900 per year in the U.S.

**R/R B-Cell NHL Response Rates:**
*ZUMA-1 Trial – December 2018*
- Objective Response Rate: 83%
- Complete Response Rate: 58%
## Select Anticipated Data Readouts: 2019

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Therapeutic Modality</th>
<th>Indication</th>
<th>Clinical Stage</th>
<th>Expected Reporting Date</th>
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<tr>
<td>GenSight Biologics</td>
<td>GS010</td>
<td>AAV-vector Gene Therapy</td>
<td>Leber Hereditary Optic Neuropathy</td>
<td>Ph III</td>
<td>Topline data Q1 2019</td>
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<td>Astellas</td>
<td>AST-OPC1</td>
<td>Stem cell therapy</td>
<td>Severe spinal cord injury</td>
<td>Ph I/IIA</td>
<td>12 month results Q1 2019</td>
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<td>Athersys</td>
<td>MultiStem</td>
<td>Cell therapy</td>
<td>Acute respiratory distress syndrome</td>
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<td>SBI-101</td>
<td>MSC Device</td>
<td>Acute Kidney Injury</td>
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<td>AT342</td>
<td>Gene therapy</td>
<td>Crigler-Najjar Syndrome</td>
<td>Ph I/II</td>
<td>Interim data Q1 2019</td>
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<td>AXO-AAV-GM2</td>
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<td>FCX-007</td>
<td>Gene Therapy</td>
<td>Recessive Dystrophic Epidermolysis Bullosa</td>
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<td>CLBS03</td>
<td>Cell therapy</td>
<td>Type 1 Diabetes</td>
<td>Ph II</td>
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<td>Allogeneic Mesenchymal Precursor Cell Therapy</td>
<td>Acute Myocardial Infarction</td>
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<td>ECCI-50</td>
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<td>Male stress urinary incontinence</td>
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<td>Spinal Fusion</td>
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<td>Gene therapy</td>
<td>Phenylketonuria</td>
<td>Pre-Ph I</td>
<td>Initial data 2019</td>
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Source: Company-provided or publicly-available information
Sector Financings
Total Global Financings: 2018

$13.3B  Total Global Financings 2018 ▲73% from 2017

$9.7B  Gene-Based Therapies 2018 Financings ▲64% from 2017

$7.6B  Cell Therapy 2018 Financings ▲64% from 2017

$936.9M  Tissue Engineering 2018 Financings ▲258% from 2017

Source data provided by: informa
*Both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies
Total Financings by Type, by Year

Corporate Partnerships (Upfront Payments Only)
- 2018: $1,740
- 2017: $647
- 2016: $1,121

Private Placements / PIPES
- 2018: $1,245
- 2017: $659
- 2016: $942

Follow On / Secondary Public Offering
- 2018: $3,994
- 2017: $890

IPO
- 2018: $1,927
- 2017: $254
- 2016: $594

Venture Capital
- 2018: $2,907
- 2017: $1,448
- 2016: $1,250

Source data provided by: informa
Total M&A Transactions Values, By Year

Celgene/Juno & Novartis/AveXis account for nearly 89% of total M&A
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:

- Statement released in January 2019 details plan to hire additional reviewers, leverage expedited pathways, and issue new guidances for different areas of product development of cell and gene therapies
- Two CMC specific draft guidances for cell and gene therapies released July 2018
- Disease-specific draft guidances on hemophilia, rare diseases, retinal disorders
- 28 products have received RMAT designation to date
Market Access Landscape in 8 Countries
As of January 2019

France (TC/CEESP)
- Kymriah
- Yescarta

Germany (IQWIG/G-BA)
- Alofisel
- Imlygic
- Kymriah
- Luxturna
- Strimvelis
- Yescarta
- Zalmoxis

UK (NICE/SMC)
- Holoclar

Italy (AIFA/regional)
- Holoclar
- Imlygic
- Kymriah
- Luxturna
- Strimvelis
- Yescarta
- Zalmoxis

Netherlands (ZIN/CVZ)
- Imlygic

U.S. (CMS)
- Imlygic

Canada (CADTH)
- Kymriah
  - CADTH Assessment: Would be cost effective if price lowered
- Kymriah Undergoing MSAC assessment

Australia (MSAC)
- Kymriah

Positive HTA Opinion
Reimbursed
In Summary

- 2018 was a year of significant growth in the regenerative medicine sector
- A rich and diverse pipeline is producing positive data
- The impact of early products for patients and families is dramatic
- 2018 saw pronounced investor interest in the sector
- The policy environment for cell and gene therapies is extremely positive
- 2019 will see the sector address commercialization challenges, particularly focused on new payment models and CMC considerations
Thank You!