Sector Overview

• **Clinical Progress:** 2018 YTD
• **Anticipated Clinical Data Events:** 2018 and beyond
• **Sector Financial Performance:** 2018 YTD
• **Policy Environment:** 2018
This presentation will be available via:

• **ARM’s website:** www.alliancerm.org
• **Twitter** @alliancerm
ARM’s Role in the Sector

• Advocating for clear, predictable, and harmonized regulatory and review 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 and identifying sources of potential public funding
Current Global Sector Landscape

866
Regenerative Medicine Companies Worldwide, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers

466
North America

235
Europe & Israel

127
Asia

22
Oceania
Australia, New Zealand, Marshall Islands

15
South America

1
Africa

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

- **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: nanoparticles and nanospheres

- **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.
Recent Product Approvals

Approvals in 2017:

- Spark Therapeutics’ LUXTURNA gene therapy for biallelic RPE65-mediated inherited retinal disease – Dec 19; MAA submitted to EMA – July 31
- Gilead / Kite Pharma’s Yescarta CAR T-cell therapy for the treatment of adult patients with relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy – Oct 18; MAA expected 1H 2018
- Novartis’s Kymriah CAR T-cell therapy for the treatment of children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia and for adults with r/r diffuse large B-cell – August 30; MAA submitted to EMA – Nov 6
- TissueGene’s (now Kolon TissueGene) exclusive Asia licensee Kolon Life Science’s Invossa-K Inj – July 12

Approvals YTD 2018:

- TiGenix’s Alofisel (previously Cx601) allogeneic stem cell therapy for treatment of perianal fistulas in Crohn’s disease patients received central marketing authorization from the European Commission – March 23
- Novartis’s Kymriah received FDA approval for a second indication: treatment of adult patients with r/r large B-cell lymphoma – May 1
Total Clinical Trials by Phase

Phase I: 318 (Up 18% YoY)
Phase II: 541 (Up 5% YoY)
Phase III: 93 (Up 37% YoY)

Source data provided by: informa
Total Clinical Trials by Technology Type

Gene Therapy
- Total: 310
  - Phase I: 103
  - Phase II: 172
  - Phase III: 35

Gene-Modified Cell Therapy
- Total: 292
  - Phase I: 128
  - Phase II: 151
  - Phase III: 13

Cell Therapy
- Total: 326
  - Phase I: 82
  - Phase II: 206
  - Phase III: 38

Tissue Engineering
- Total: 24
  - Phase I: 5
  - Phase II: 12
  - Phase III: 7
• **503 (52%) 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.

• **Nearly one in 10 are in cardiovascular disorders**, including congestive heart failure, myocardial infarction, critical limb ischemia, heart disease, and others.
# Select Anticipated Late-Stage Data Events: 2018+

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Kiadis</td>
<td>ATIR101</td>
<td>Allo-depleted T-Cell Immunotherapy</td>
<td>AML or ALL</td>
<td>Conditional EU approval</td>
<td>2H 2018; launch 2019</td>
</tr>
<tr>
<td>bluebird bio</td>
<td>Lentiglobin</td>
<td>Gene therapy</td>
<td>Transfusion dependent beta-thalassemia</td>
<td>MAA filing</td>
<td>End-year 2018</td>
</tr>
<tr>
<td>Kite (Gilead co)</td>
<td>Yescaarta</td>
<td>CD19-directed CAR T cell therapy</td>
<td>Refractory Large B-Cell Lymphoma</td>
<td>Pending MAA</td>
<td>1H 2018</td>
</tr>
<tr>
<td>Enzyvant Tx</td>
<td>RVT-802</td>
<td>Tissue-based therapy</td>
<td>Complete DiGeorge Syndrome</td>
<td>BLA submission</td>
<td>2018</td>
</tr>
<tr>
<td>Juno Therapeutics</td>
<td>JCAR017</td>
<td>CAR-T cell therapy</td>
<td>NHL</td>
<td>BLA submission</td>
<td>2H 2018</td>
</tr>
<tr>
<td>Abeona</td>
<td>EB-101</td>
<td>Gene therapy</td>
<td>Epidermolysis Bullosa</td>
<td>Ph III</td>
<td>Trial commences 2018</td>
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<tr>
<td>Athersys</td>
<td>MultiStem</td>
<td>Cell therapy</td>
<td>Ischemic Stroke</td>
<td>Ph III (under SPA)</td>
<td>Initiating 1H 2018</td>
</tr>
<tr>
<td>BioMarin</td>
<td>Valoctocogene roxaparvovec</td>
<td>Gene therapy</td>
<td>Hemophilia A</td>
<td>Ph III</td>
<td>Trial update expected at World Federation of Hemophilia 2018 World Congress, May 2018</td>
</tr>
<tr>
<td>bluebird bio</td>
<td>Lentiglobin</td>
<td>Gene therapy</td>
<td>Transfusion dependent beta-thalassemia</td>
<td>Ph III – Northstar-2 HGB-207</td>
<td>Mid-year 2018</td>
</tr>
<tr>
<td>bluebird bio</td>
<td>Lentiglobin</td>
<td>Gene therapy</td>
<td>Transfusion dependent beta-thalassemia &amp; beta-0/beta-0 genotypes</td>
<td>Ph III – Northstar-3 (HGB-212)</td>
<td>End-year 2018</td>
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<tr>
<td>bluebird bio</td>
<td>Lenti-D</td>
<td>Gene therapy</td>
<td>Cerebral Adrenoleukodystrophy</td>
<td>Ph III – Starbeam 102</td>
<td>End-year 2018</td>
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<tr>
<td>Bone Therapeutics</td>
<td>PREOB</td>
<td>Cell therapy (autologous)</td>
<td>Osteonecrosis of the hip</td>
<td>Ph III</td>
<td>2H 2018</td>
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<tr>
<td>Brainstorm</td>
<td>NurOwn</td>
<td>Mesenchymal Stem Cell Therapy</td>
<td>ALS</td>
<td>Ph III</td>
<td>Interim safety data June 2018; top-line data 2019</td>
</tr>
</tbody>
</table>

Source: Company-provided or publicly-available information
### Select Anticipated Late-Stage Data Events: 2018+

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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 (REVERSE &amp; RESCUE)</td>
<td>Topline results of REVERSE in Q2 2018 (announced 04/03/18); RESCUE in Q3 2018</td>
</tr>
<tr>
<td>Histogenics</td>
<td>NeoCart</td>
<td>Tissue-engineering product</td>
<td>Knee cartilage repair</td>
<td>Ph III (topline data, potential BLA filing)</td>
<td>Q3 2018</td>
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<td>Mesoblast</td>
<td>MPC-150-IM</td>
<td>Mesenchymal Precursor Cell Therapy</td>
<td>Moderate to Severe Chronic Heart Failure</td>
<td>Ph III</td>
<td>Complete enrollment 2H CY 2018</td>
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<tr>
<td>Mesoblast</td>
<td>MSC-100-IV</td>
<td>Mesenchymal Stem Cell Therapy</td>
<td>Acute Graft Versus Host Disease</td>
<td>Ph III</td>
<td>Day 100 survival Q2 CY 2018; Day 180 safety data Q3 CY 2018</td>
</tr>
<tr>
<td>Mesoblast</td>
<td>MPC-06-ID</td>
<td>Mesenchymal Precursor Cell Therapy</td>
<td>Chronic Low Back Pain Due to Disc Degeneration</td>
<td>Ph III</td>
<td>Enrollment completed Q1 CY 2018</td>
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<tr>
<td>Nightstar Therapeutics</td>
<td>NSR-REP1</td>
<td>Gene therapy</td>
<td>Choroideremia</td>
<td>Ph III</td>
<td>Complete enrollment 1H 2019</td>
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<tr>
<td>AveXis</td>
<td>AVXS-101</td>
<td>Gene Therapy</td>
<td>Spinal Muscular Atrophy Type 1</td>
<td>Pivotal (Str1VE EU)</td>
<td>European trial expected to be initiated in H1 2018</td>
</tr>
<tr>
<td>uniQure</td>
<td>AMT-061</td>
<td>AAV Gene Therapy</td>
<td>Hemophilia B</td>
<td>Pivotal</td>
<td>Dose-confirmation study to begin Q2 2018; topline data expected EOY 2018; lead-in will start Q3 2018; dosing in pivotal trial will follow.</td>
</tr>
<tr>
<td>Athersys-Healios KK</td>
<td>MultiStem</td>
<td>Cell therapy</td>
<td>Ischemic Stroke (Japan)</td>
<td>Ph II/III</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Lysogene</td>
<td>LYS-SAF302</td>
<td>Gene therapy</td>
<td>MPS IIIA</td>
<td>Ph II/III</td>
<td>Enrollment 2H 2018</td>
</tr>
</tbody>
</table>

Source: Company-provided or publicly-available information
Total Global Financings: As of Mid-May 2018

$5.6B Total Global YTD 2018 Financings 141% increase YoY

$4.6B Gene-Based Therapies YTD 2018 Financings 210% increase YoY

$2.8B Cell Therapy YTD 2018 Financings 85% increase YoY

$486.1M Tissue Engineering YTD 2018 Financings 572% increase YoY

*both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies

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

- **Corporate Partnerships (Upfront Payments Only)**
  - YTD 2018: $704, Full-year 2017: $1,086
  - YTD 2018: $647, Full-year 2016: $970
  - Full-year 2015: $2,216

- **Private Placement / PIPES**
  - YTD 2018: $393, Full-year 2017: $661
  - Full-year 2016: $884, Full-year 2015: $970
  - YTD 2018: $2,730, Full-year 2017: $3,989

- **Follow On / Secondary Public Offering**
  - YTD 2018: $286, Full-year 2017: $588
  - Full-year 2016: $884, Full-year 2015: $970
  - YTD 2018: $2,244, Full-year 2017: $3,000

- **IPO**
  - YTD 2018: $254, Full-year 2017: $588
  - Full-year 2016: $1,409, Full-year 2015: $1,653
  - YTD 2018: $1,484, Full-year 2017: $1,909

- **Venture Capital**
  - YTD 2018: $1,409, Full-year 2017: $1,260
  - Full-year 2016: $1,909, Full-year 2015: $1,909
  - YTD 2018: $1,484, Full-year 2017: $1,909

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

YTD 2018 already 68% of full-year 2017
Select Corporate Partnerships & Public Financings: YTD 2018

Corporate Partnerships: (Upfront Payments)

• Kite Pharma signs $3.1B agreement with Sangamo Therapeutics, $150M upfront – Feb 20
• Spark Therapeutics signs $110M agreement with Jazz Pharmaceuticals, all upfront – April 30
• Spark Therapeutics signs agreement $170M agreement with Novartis, incl $105M upfront – Jan 24
• REGENXBIO & AveXis $260M amended license agreement, $80M upfront – Jan 8
• AbbVie signs $1.1B agreement with Voyager, incl $69M upfront – Feb 16

Private Placements & Venture Financings:

• Allogene $300M Series A – April 3
• Celularity $250M – Feb 15
• Rubius Therapeutics $100M – March 1
• TCR2 $125M Series B – March 21
• Tmunity Therapeutics $100M Series A – Jan 23
• Generation Bio $100M Series B - Feb 27
• CARsgen Therapeutics $60M – March 2
• Tessa Therapeutics $50M – April 11

Public Offerings: (IPOs & Follow-Ons)

• bluebird bio $651.3M – Jan 8
• AveXis $431.9M – Jan 22
• Audentes $231.4M – Jan 29
• Sangamo Therapeutics $230M – April 30
• Cellectis $190.5M - April 10
• Iovance Biotherapeutics - $172.5M – Jan 29
• Homology Medicines - $165.6M – April 3
• uniQure $147.5M – May 7
• Solid Biosciences $143.8M IPO – Jan 30
• CRISPR Therapeutics $130.8M – Jan 9
• AxoGen $123M – May 7
Supportive Policy Environment

U.S.:

• Sector supportive U.S. FDA Commissioner Scott Gottlieb:
  • “I believe we’re at a turning point when it comes to gene therapy. Over the next several years, we’ll see this approach become a mainstay of treating, and probably curing, a lot of our most devastating and intractable illnesses. At FDA, we’re focused right now on establishing the right policy framework to capitalize on this scientific opening.”
    - Testimony before the U.S. Senate HELP Committee on the agency’s implementation of the 21st Century Cures Act, December 7, 2017

• FDA’s RMAT Designation:
  • Enacted in December 2016 as part of the 21st Century Cures Act
  • Acknowledges the importance and unique characteristics of RM technologies
  • Provides for expedited approval without weakening FDA’s strong safety and efficacy standards.

Europe:

• European Commission and EMA developing ATMP plan of action, with ARM providing input on proposals
• European Commission encouraging concerted effort region-wide regarding aspects of Health Technology Assessment
FDA’s RMAT Designation

Product sponsor benefits:
• Guaranteed interactions with the FDA.
• Eligibility for priority review and accelerated approval.
• Flexibility in the number of clinical sites used and the possibility to use patient registry data and other sources of “real-world” evidence for post-approval studies (pending FDA approval).

Implementation:
• In early 2017, FDA published application instructions.
• ARM’s February RMAT webinar for members included FDA officials.
• ARM advocated that gene therapies qualify; FDA confirmed late 2017.
• 16 products have publicly announced they have received the designation (as of mid-May 2018); including 2 gene therapy products.
# FDA’s RMAT Designation

## U.S. FDA RMAT Designations – YTD 2018

<table>
<thead>
<tr>
<th>No.</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abeona’s EB-101 (recessive dystrophic EB)</td>
</tr>
<tr>
<td>2</td>
<td>Abeona’s ABO-102 AAV gene therapy (MPS IIIA)</td>
</tr>
<tr>
<td>3</td>
<td>Asterias’s AST-OPC1 (spinal cord injury)</td>
</tr>
<tr>
<td>4</td>
<td>Athersys’s MultiStem (ischemic stroke)</td>
</tr>
<tr>
<td>5</td>
<td>bluebird bio’s LentiGlobin (severe sickle cell disease)</td>
</tr>
<tr>
<td>6</td>
<td>Capricor CAP-1002 (Duchenne muscular dystrophy)</td>
</tr>
<tr>
<td>7</td>
<td>Cellvation’s CEVA101 (traumatic brain injury)</td>
</tr>
<tr>
<td>8</td>
<td>Enzyvant’s RVT-802 (DiGeorge syndrome)</td>
</tr>
<tr>
<td>9</td>
<td>Humacyte’s Humacryl (vascular access for hemodialysis)</td>
</tr>
<tr>
<td>10</td>
<td>jCyte’s jCell (retinitis pigmentosa)</td>
</tr>
<tr>
<td>11</td>
<td>Juno’s JCAR017 (r/r aggressive large B cell NHL)</td>
</tr>
<tr>
<td>12</td>
<td>Kiadis’s ATIR101 (leukemia)</td>
</tr>
<tr>
<td>13</td>
<td>Mallinckrodt’s Stratagraft (deep partial-thickness burns)</td>
</tr>
<tr>
<td>14</td>
<td>Mesoblast’s MPC-150-IM (heart failure)</td>
</tr>
<tr>
<td>15</td>
<td>MiMedx’s AmnioFix (osteoarthritis of the knee)</td>
</tr>
<tr>
<td>16</td>
<td>Vericel’s ixmyelocel (dilated cardiomyopathy)</td>
</tr>
</tbody>
</table>
Current Activity

Companies and payers exploring value-based payment models, for example:

**Spark:**
- Outcomes-based rebate arrangement w/ long-term durability measure for Luxturna
- Proposal to CMS for an annuity-based payment model

**Novartis:**
- Collaboration with CMS on outcomes-based approach for Kymriah
- Discussing value-based approaches for additional Kymriah indication & other CAR T-cell therapies

**CMS Proposed Rule:**
- ARM working with CMS to reform Medicare’s program to cover new technologies in the Inpatient Prospective Payment System, enabling patient access to RM / AT products, including CAR T-cell therapies
- Proposed rule released April 24 is encouraging, demonstrates flexibility
ARM’s Strategic Focus Areas

Regulatory

• Promote clear, predictable, and efficient regulatory framework.
• Assess all FDA, EMA, and related guidance relevant to cell and gene therapy, including guidance related to manufacturing, CMC, and related issues.
• Drive international convergence of key regulation and guidance to promote global product development by identifying specific areas of regulatory inconsistency.

Reimbursement

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

Industrialization and Manufacturing

• Reduce standards, technical, and regulatory barriers to scale up of RM / AT therapies.
Key Takeaways

Supportive policy environment:
• U.S. and globally

Strong scientific data:
• Potential for positive, widespread patient impact
• Significant near-term late-stage anticipated clinical milestones

Sustained investor interest:
• Substantial year-over-year increases across financing types
• Strong M&A activity; additional activity anticipated

Commercial opportunities and challenges:
• Transformative products on the market; many more to come near-term
• Success dependent on addressing market access, regulatory convergence, and industrialization issues
Thank You!