State of the Industry

Cell & Gene Therapy Sector Update

Janet Lambert, CEO
18 October 2018
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*
State of the Industry Briefing

- Global Sector Overview: 2018
- Clinical Progress: YTD 2018
- Anticipated Clinical Data Events: 2018+
- Sector Financings: YTD 2018
- Reimbursement Environment
This presentation will be available via:

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

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

- North America: 476
- South America: 15
- Europe & Israel: 235
- Asia: 142
- Africa: 1
- Oceania: 23

Source data provided by: informa
European Sector Overview

235 Regenerative Medicine Companies in Europe, including Gene and Cell Therapies, and Tissue Engineering Therapeutic Developers
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 YTD 2018:

• Spark Therapeutics’ **LUXTURNA** gene therapy for biallelic RPE65-mediated inherited retinal disease received positive CHMP opinion – September 21

• Avita Medical’s **RECELL** system 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

• Novartis’s **Kymriah** 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

• TiGenix’s (now Takeda’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
Total Clinical Trials by Phase - End Q3 2018

Phase I
330
7.5% increase YoY

Phase II
580
6% increase YoY

Phase III
93
18% increase YoY

Source data provided by: informa
Total Clinical Trials by Technology Type – End Q3 2018

Gene Therapy
Total: 351
Phase I: 114
Phase II: 204
Phase III: 33

Gene-Modified Cell Therapy
Total: 328
Phase I: 145
Phase II: 168
Phase III: 15

Cell Therapy
Total: 283
Phase I: 61
Phase II: 189
Phase III: 33

Tissue Engineering
Total: 41
Phase I: 10
Phase II: 19
Phase III: 12

Source data provided by: informa
• **57% (573)** 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% (69)** 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
<table>
<thead>
<tr>
<th><strong>Company</strong></th>
<th><strong>Product</strong></th>
<th><strong>Therapeutic Modality</strong></th>
<th><strong>Indication</strong></th>
<th><strong>Clinical Stage</strong></th>
<th><strong>Expected Reporting Date</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiadis</td>
<td>ATIR101</td>
<td>Allodepleted T-Cell Immunotherapy</td>
<td>AML or ALL</td>
<td>Conditional EU approval</td>
<td>On track to receive CHMP opinion Q4 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>EMA accepted MAA; will be evaluated under accelerated assessment, decision expected 2019</td>
</tr>
<tr>
<td>Orchard Therapeutics</td>
<td>OTL-200</td>
<td>Gene therapy</td>
<td>metachromatic leukodystrophy</td>
<td>MAA filing</td>
<td>To file MAA 2020, followed by a BLA with the FDA</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>Initiation of rolling BLA submission in July 2018; BLA expected to be completed in 2018</td>
</tr>
<tr>
<td>Juno/Celgene</td>
<td>Liso-cel</td>
<td>CAR-T cell therapy</td>
<td>NHL</td>
<td>BLA submission</td>
<td>2H 2018</td>
</tr>
<tr>
<td>PTC Therapeutics</td>
<td>GT-AADC</td>
<td>Gene therapy</td>
<td>AADC Deficiency</td>
<td>BLA submission</td>
<td>Expects to submit BLA in 2019</td>
</tr>
<tr>
<td>bluebird bio / Celgene</td>
<td>bb21217</td>
<td>CAR-T</td>
<td>third line multiple myeloma</td>
<td>Ph III</td>
<td>Study to be initiated by Celgene in 2H 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>
</tr>
<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>
</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>
</tr>
<tr>
<td>Athersys</td>
<td>MultiStem</td>
<td>Cell therapy</td>
<td>Ischemic Stroke</td>
<td>Ph III (under SPA)</td>
<td>Initiating 2018</td>
</tr>
<tr>
<td>AveXis</td>
<td>AVXS-101</td>
<td>Gene Therapy</td>
<td>Pediatric SMA Types 1, 2, and 3</td>
<td>Ph III</td>
<td>Expected to initiate in late Q4 2018 or early 2019.</td>
</tr>
<tr>
<td>BioMarin</td>
<td>Valoctocogene roxaparvovec</td>
<td>Gene therapy</td>
<td>Hemophilia A</td>
<td>Ph III</td>
<td>Increase in enrollment to 130 participants anticipated by 1Q 2019.</td>
</tr>
</tbody>
</table>
Total Global Financings: Q3 2018

<table>
<thead>
<tr>
<th>Category</th>
<th>Total Global Financings Q3 2018</th>
<th>Increase from Q3 2017</th>
<th>YOY Increase (YTD 2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Global</td>
<td>€2.4B</td>
<td>59%</td>
<td>40% (€9.2B)</td>
</tr>
<tr>
<td>Financings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene-Based Therapies</td>
<td>€1.8B</td>
<td>35%</td>
<td>34% (€6.7B)</td>
</tr>
<tr>
<td>Q3 2018 Financings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell Therapy</td>
<td>€1.6B</td>
<td>73%</td>
<td>32% (€5.2B)</td>
</tr>
<tr>
<td>Q3 2018 Financings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue Engineering</td>
<td>€1.3M</td>
<td>91%</td>
<td>213% (€678.3M)</td>
</tr>
<tr>
<td>Q3 2018 Financings</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)

Private Placement / PIPES

Follow On / Secondary Public Offering

IPO

Venture Capital

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

YTD 2018 has already surpassed full-year 2017

Source data provided by: informa
Select Corporate Partnerships & Public Financings: YTD 2018

Corporate Partnerships: (Upfront Payments)
• Genmab signs €47M upfront agreement with Immatics – July 12
• Mesoblast signs €35M upfront agreement with Tasly – July 17
• bluebird bio signs €26M upfront agreement with Gritstone Oncology – August 23
• Allergan exercises €13M upfront option agreement with Editas Medicine – August 6
• CRISPR Therapeutics signs €13M upfront agreement with ViaCyte – September 17

Private Placements & Venture Financings:
• Orchard Therapeutics €130M Series C – August 13
• Allogene €104M Venture Financing – September 6
• bluebird bio €86M Private Placement – August 6
• 4D Molecular Tx €78M Venture Financing – September 5
• SQZ Biotechnologies €62M Venture Financing – August 8
• Ambys Medicines €52M Series A – August 8
• Akouos €43M Series A – August 7
• AgeX €37M Private Placement – September 4
• SCM Lifescience €30M Series C – September 7
• Recombinetics €29M Private Placement – August 21
• Lacerta Tx €26M Private Placement – August 8

Public Offerings: (IPOs & Follow-On Financings)
• bluebird bio €546M follow-on financing – July 27
• Rubius Tx €239M initial public offering – July 23
• REGENXBIO €174M follow-on financing – August 14
• CRISPR Tx €173M follow-on financing – September 19
• Fate Tx €124M follow-on financing – September 25
• Adaptimmune €86M follow-on financing – September 7

M&A Activity: (Upfront Payments)
• Takeda acquires TiGenix for €540M upfront – July 31
• PTC Tx acquires Agilis for €173M upfront – August 23
• Astellas acquires Quethera for €93M upfront – August 10
<table>
<thead>
<tr>
<th>Gene Therapies</th>
<th>Cell Therapies</th>
<th>Tissue Therapies</th>
</tr>
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<tbody>
<tr>
<td><strong>Glybera X</strong></td>
<td>- Non-quantifiable added benefit</td>
<td>-</td>
</tr>
<tr>
<td><strong>Imlygic</strong></td>
<td>- No added benefit but reimbursed</td>
<td>PAS</td>
</tr>
<tr>
<td><strong>Strimvelis</strong></td>
<td>- -</td>
<td>Hospital only, innovative status, annuity payment by results</td>
</tr>
<tr>
<td><strong>Kymriah</strong></td>
<td>- -</td>
<td>Contract with NHS</td>
</tr>
<tr>
<td><strong>Yescarta</strong></td>
<td>- -</td>
<td>Negative NICE Draft Guidance</td>
</tr>
<tr>
<td><strong>Luxturna</strong></td>
<td>- -</td>
<td>-</td>
</tr>
<tr>
<td><strong>Provenge X</strong></td>
<td>- Non-quantifiable added benefit</td>
<td>-</td>
</tr>
<tr>
<td><strong>Zalmoxis</strong></td>
<td>- Non-quantifiable added benefit</td>
<td>-</td>
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<tr>
<td><strong>Alofisel</strong></td>
<td>- Non-quantifiable added benefit</td>
<td>Negative NICE Draft Guidance</td>
</tr>
<tr>
<td><strong>Chondrocelect X</strong></td>
<td>Not eligible for EBA</td>
<td>Negative NICE Guidance</td>
</tr>
<tr>
<td><strong>MACI X</strong></td>
<td>Not eligible for EBA</td>
<td>Negative NICE Guidance</td>
</tr>
<tr>
<td><strong>Holoclar</strong></td>
<td>Not eligible for EBA</td>
<td>PAS</td>
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</table>

Key:
- Reimbursed
- Not reimbursed
- Withdrawn from market

**Gene Therapies:**
- Glybera: Non-quantifiable added benefit
- Imlygic: No added benefit but reimbursed
- Strimvelis: Hospital only, innovative status, annuity payment by results
- Kymriah: Contract with NHS
- Yescarta: Negative NICE Draft Guidance
- Luxturna: Hospital only
- Provenge: Non-quantifiable added benefit
- Zalmoxis: Non-quantifiable added benefit
- Alofisel: Negative NICE Draft Guidance
- Chondrocelect: Not eligible for EBA
- MACI: Not eligible for EBA
- Holoclar: Hospital only payment by results

**Cell Therapies:**
- **Yescarta:** Reimbursed
- **Kymriah:** Not reimbursed
- **Luxturna:** Hospital only
- **Provenge:** Hospital only
- **Zalmoxis:** Hospital only
- **Alofisel:** Hospital only
- **Chondrocelect:** Hospital only
- **MACI:** Hospital only
- **Holoclar:** Hospital only

**Tissue Therapies:**
- **Glybera:** Non-quantifiable added benefit
- **Imlygic:** No added benefit but reimbursed
- **Strimvelis:** Hospital only, innovative status, annuity payment by results
- **Kymriah:** Contract with NHS
- **Yescarta:** Negative NICE Draft Guidance
- **Luxturna:** Hospital only
- **Provenge:** Hospital only
- **Zalmoxis:** Hospital only
- **Alofisel:** Hospital only
- **Chondrocelect:** Hospital only
- **MACI:** Hospital only
- **Holoclar:** Hospital only

**Key:**
- HTA Negative opinion
- HTA positive opinion
- HTA positive opinion with limitations

As of September 2018; Adapted from Creativ-Ceutical’s EU market access landscape assessment for ARM
Landscape Summary

**Supportive policy environment:**
- U.S., EU, and globally

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

**Sustained investor, partnering interest:**
- Substantial year-over-year increases across financing types
- Significant increase in IPO activity
- Strong M&A activity; additional activity anticipated

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

This presentation & more information can be found via:

• ARM’s website: www.alliancerm.org
• Twitter @alliancerm