State of the Industry

Mid-Year Update

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Alliance *for* Regenerative Medicine

Sector Overview

- **Clinical Progress:** 2018 YTD
- **Anticipated Clinical Data Events:** 2018 and beyond
- **Sector Financial Performance:** 2018 YTD
- **Policy Environment:** 2018

A Quick Note -

This presentation will be available via:

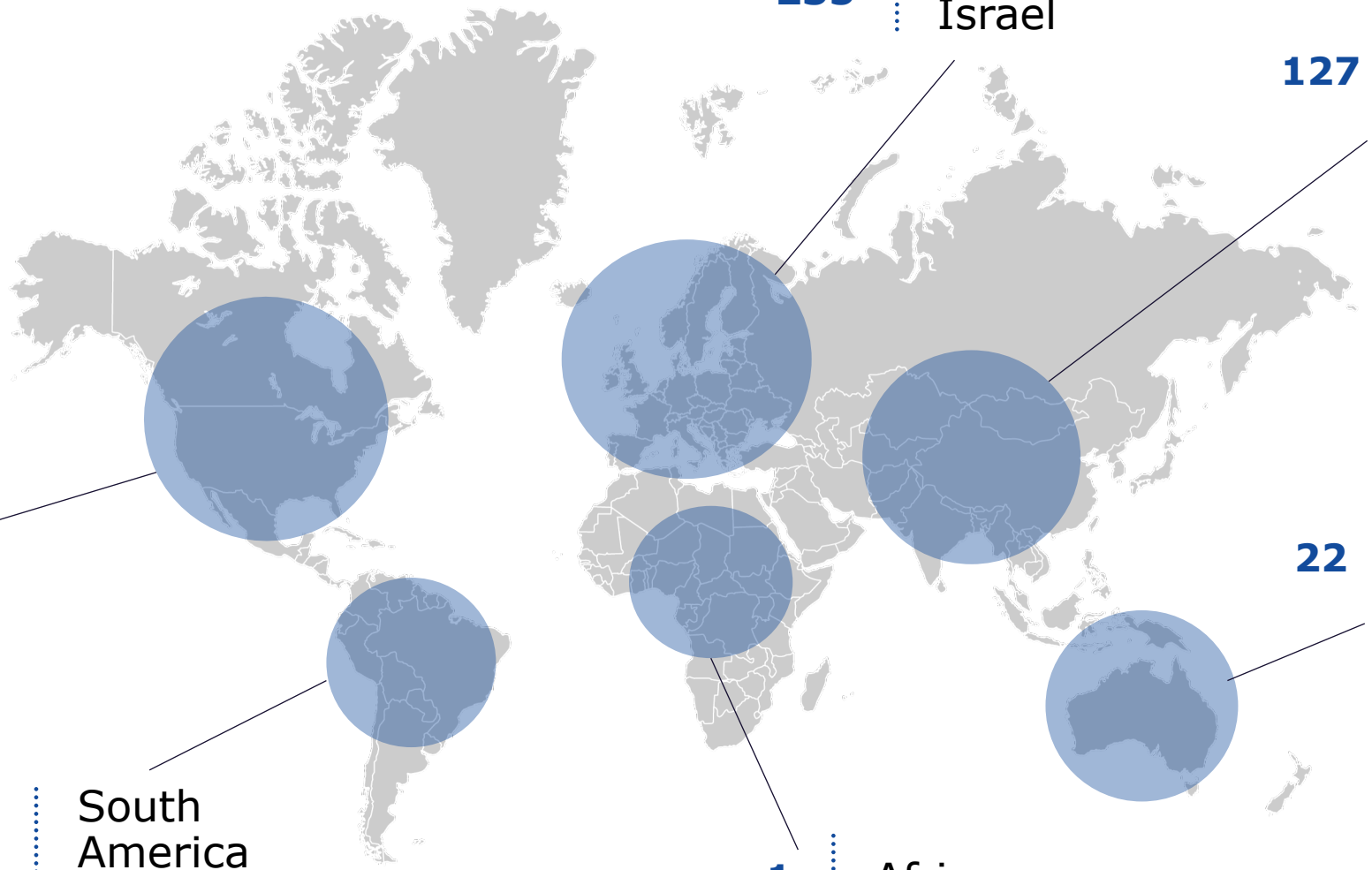
- **ARM's website: www.alliancerm.org**
- **Twitter @alliancerm**

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

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- **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

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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

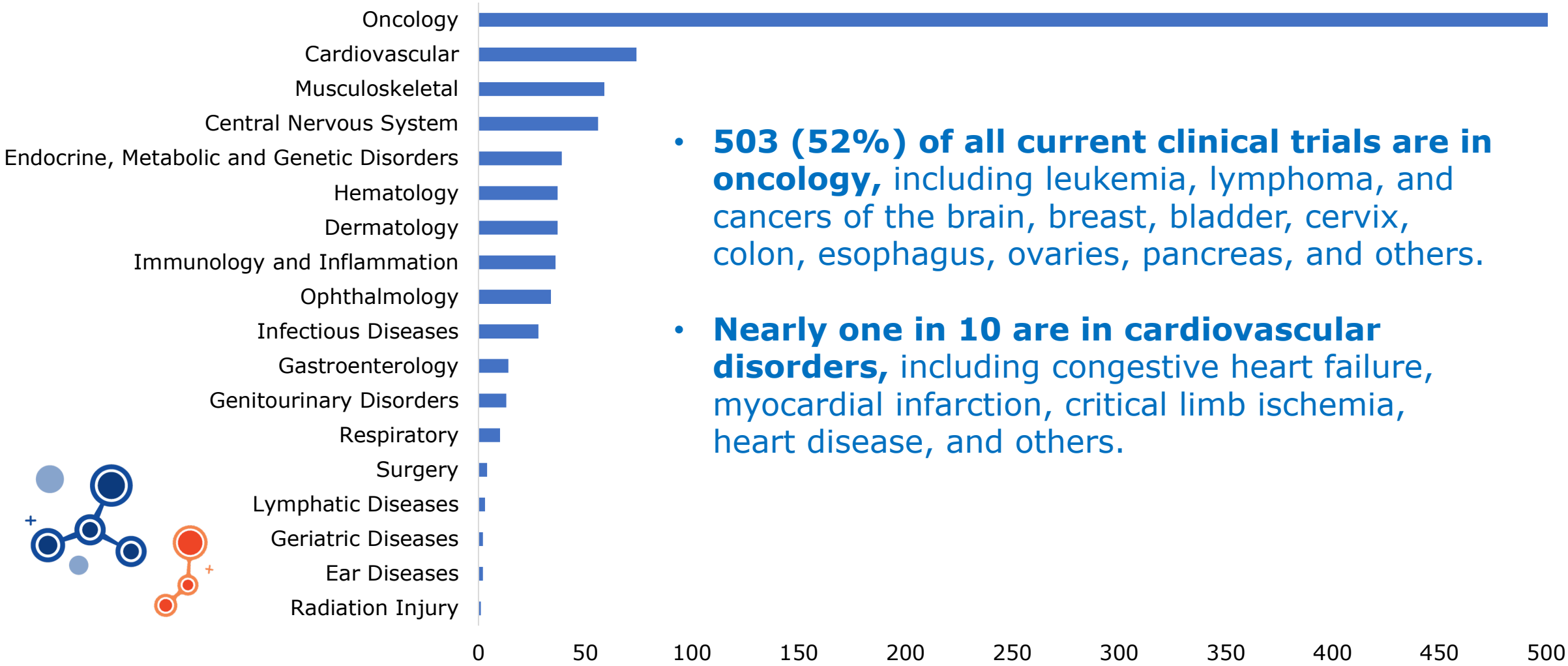
Phase I: 5

Phase II: 12

Phase III: 7

Source data provided by: informa

Clinical Trials by Therapeutic Category



- **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.

Source data provided by: informa

Select Anticipated Late-Stage Data Events: 2018+

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

Source: Company-provided or publicly-available information

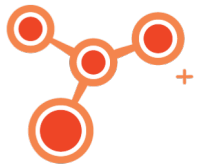
Select Anticipated Late-Stage Data Events: 2018+

Alliance for Regenerative Medicine

Company	Product	Therapeutic Modality	Indication	Clinical Stage	Expected Reporting Date
GenSight Biologics	GS010	AAV-vector Gene Therapy	Leber Hereditary Optic Neuropathy	Ph III (REVERSE & RESCUE)	Topline results of REVERSE in Q2 2018 (announced 04/03/18); RESCUE in Q3 2018
Histogenics	NeoCart	Tissue-engineering product	Knee cartilage repair	Ph III (topline data, potential BLA filing)	Q3 2018
Mesoblast	MPC-150-IM	Mesenchymal Precursor Cell Therapy	Moderate to Severe Chronic Heart Failure	Ph III	Complete enrollment 2H CY 2018
Mesoblast	MSC-100-IV	Mesenchymal Stem Cell Therapy	Acute Graft Versus Host Disease	Ph III	Day 100 survival Q2 CY 2018; Day 180 safety data Q3 CY 2018
Mesoblast	MPC-06-ID	Mesenchymal Precursor Cell Therapy	Chronic Low Back Pain Due to Disc Degeneration	Ph III	Enrollment completed Q1 CY 2018
Nightstar Therapeutics	NSR-REP1	Gene therapy	Choroideremia	Ph III	Complete enrollment 1H 2019
AveXis	AVXS-101	Gene Therapy	Spinal Muscular Atrophy Type 1	Pivotal (Str1VE EU)	European trial expected to be initiated in H1 2018
uniQure	AMT-061	AAV Gene Therapy	Hemophilia B	Pivotal	Dose-confirmation study to begin Q2 2018; topline data expected EOY 2018; lead-in will start Q3 2018; dosing in pivotal trial will follow.
Athersys-Healios KK	MultiStem	Cell therapy	Ischemic Stroke (Japan)	Ph II/III	Ongoing
Lysogene	LYS-SAF302	Gene therapy	MPS IIIA	Ph II/III	Enrollment 2H 2018

Source: Company-provided or publicly-available information

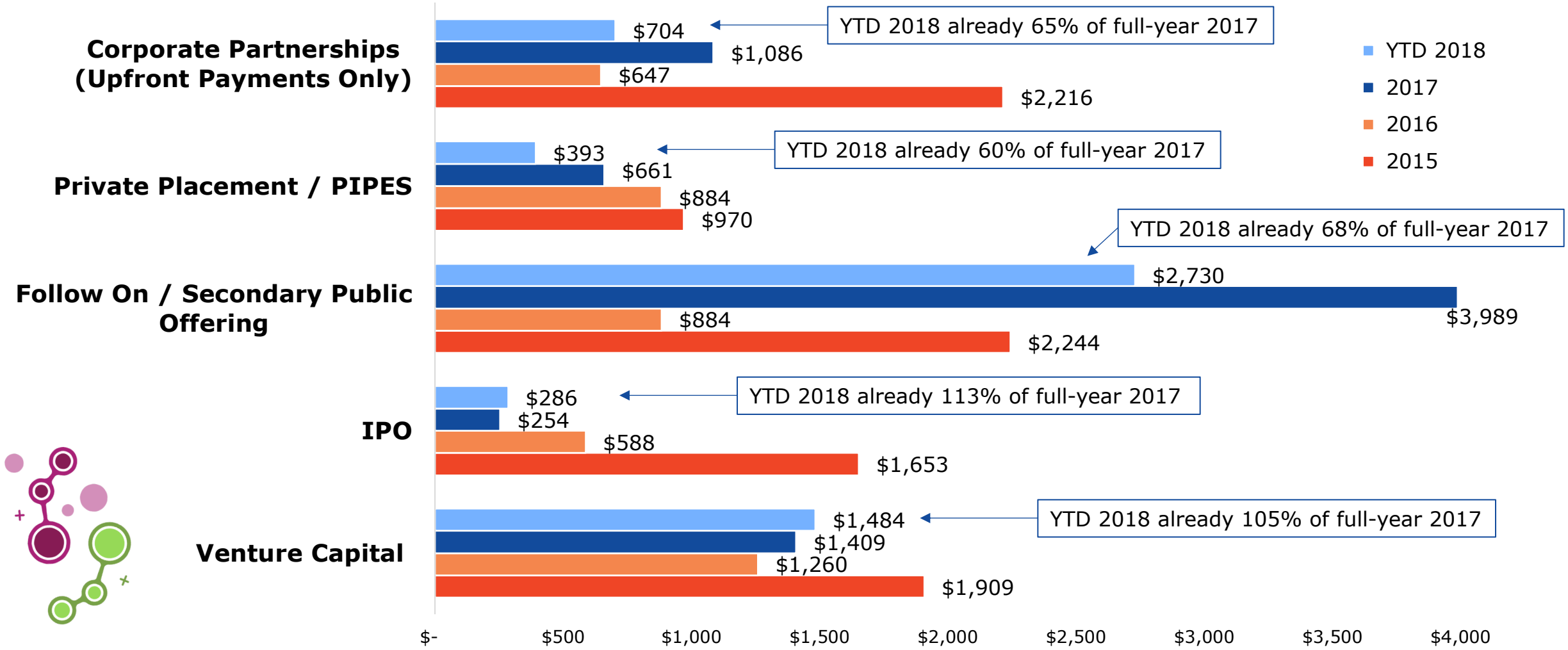
Total Global Financings: As of Mid-May 2018

	**$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

Source data provided by: informa

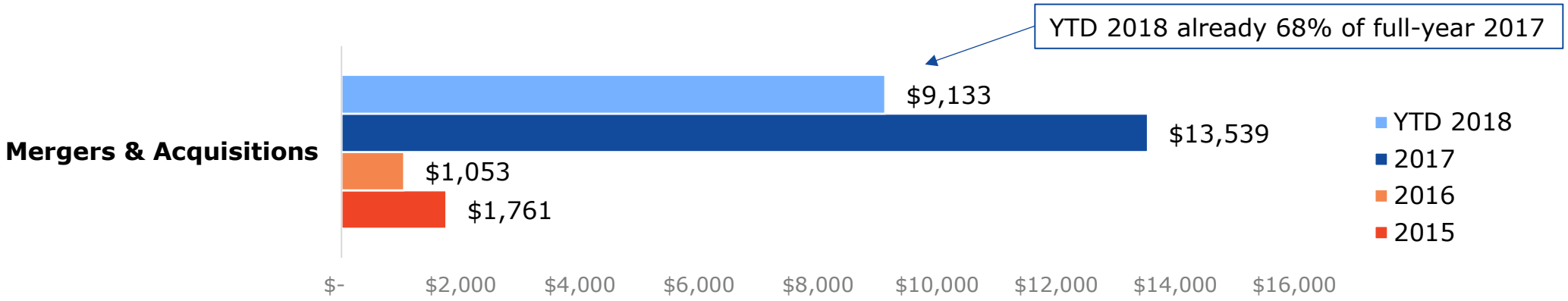
**both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies*

Total Financings by Type, by Year



Source data provided by: informa

Total M&A Transactions Values, By Year



Source data provided by: informa

Select Corporate Partnerships & Public Financings: YTD 2018

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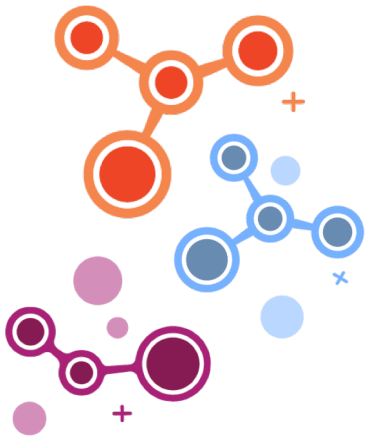
Corporate Partnerships: (Upfront Payments)

- 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

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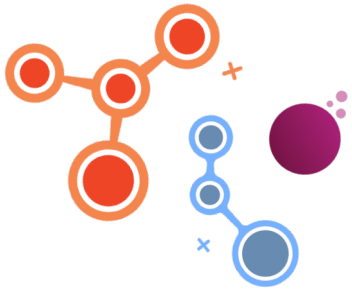
Product sponsor benefits:

- 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:

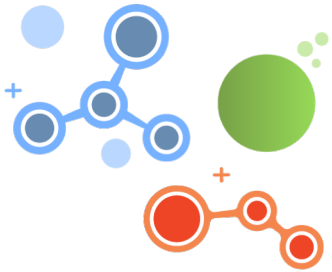
- In early 2017, FDA published application instructions.
- ARM's February RMAT webinar for members included FDA officials.
- ARM advocated that gene therapies qualify; FDA confirmed late 2017.
- 16 products have publicly announced they have received the designation (as of mid-May 2018); including 2 gene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

U.S. FDA RMAT Designations – YTD 2018

1. Abeona's EB-101 (recessive dystrophic EB)
2. Abeona's ABO-102 AAV gene therapy (MPS IIIA)
3. Asterias's AST-OPC1 (spinal cord injury)
4. Athersys's MultiStem (ischemic stroke)
5. bluebird bio's LentiGlobin (severe sickle cell disease)
6. Capricor CAP-1002 (Duchenne muscular dystrophy)
7. Cellvation's CEVA101 (traumatic brain injury)
8. Enzyvant's RVT-802 (DiGeorge syndrome)
9. Humacyte's Humacyl (vascular access for hemodialysis)
10. jCyte's jCell (retinitis pigmentosa)
11. Juno's JCAR017 (r/r aggressive large B cell NHL)
12. Kiadis's ATIR101 (leukemia)
13. Mallinckrodt's Stratagraft (deep partial-thickness burns)
14. Mesoblast's MPC-150-IM (heart failure)
15. MiMedx's AmnioFix (osteoarthritis of the knee)
16. Vericel's ixmyelocel (dilated cardiomyopathy)

Market Access Environment

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!

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