Cell & Gene Therapy Sector Overview

Lyndsey Scull
Vice President, Communications

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Alliance *for* Regenerative Medicine

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**

Alliance for Regenerative Medicine

ARM Membership

***Members in bold are publicly traded companies*

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4D Molecular Tx AABB AATB **Abeona Tx** Accelerated Bio Acera Surgical ACF Bioservices ACRO **Adaptimmune Adverum Bio** Aegle Tx **AGTC** Akron Biotech Albumedix Aldevron Alpha-1 Foundation American Gene Technologies Andalusian Initiative for Advanced Therapies ANEMOCYTE Angiocrine Bio ASGCT Aspect Biosystems ASPS Asset Mgmt Company **Astellas Asterias Atara Bio Athersys Audentes Tx** AusBiotech **Autolus** Avectas Avery Tx **Avita Medical** AVM Biotech **AVROBIO AxoGen Axovant** B-MoGen Baylor College of Medicine Be the Match Biotherapies **Becton Dickinson Bellicum Benitec** BioBridge Global **BioCardia BioLife BioMarin BioStage** Biotech Mountains **BioTime** BCA BlueRock Tx **bluebird bio Bone Tx BrainStorm Cell Tx** BrainXell Brammer Bio C3i **Caladrius Capricor Cardinal Health** Caribou Bio Carisma Tx Carpenter Consulting Casebia CASS CCRM CCTA **Celgene / Juno** Celixir Cell Medica Cell Therapies Pty Ltd Cellerant CellGenix Cells for Cells Cellular Technology Ltd Celonic Celsense CGT Catapult Chemelot CIRM City of Hope Cleveland Clinic Cleveland Cord Blood Center ClinicalMind Cognate BioServices **CombiGene** Cornell University CRC Oncology **CRISPR Tx Cryoport Systems CSL** CTI CTM CRC **Cynata Tx** Dark Horse Consulting Defined Health DiscGenics Dyno Tx EB Research Partnership **Editas Medicine Enochian Biosciences** Enzyvant Tx ERA Consulting Ltd ESGCT EveryLife Foundation Evidera ExCellThera Falcon Tx FARA **Fate Tx** FBRI **Fibrocell** Fight Colorectal Cancer **Flexion Tx** FloDesign Fondazione Telethon Fraunhofer Institute Fred Hutch Frequency Tx Froceth **FUJIFILM Cellular Dynamics** GammaDelta Tx Gates Center for Regenerative Medicine **GE Healthcare** GENETHON **GenSight Biologics** Gift of Life Marrow Registry **Gilead / Kite** Giner Global Genes Glycostem GPB Scientific Gravitas BIO **GSK Healios K.K.** Histogen **Histogenics Hitachi Chemical Adv Tx** Hogan Lovells **Homology Medicines** Hybrid Concepts International Immusoft INmune Bio InRegen Institut Clayton de la Recherche **Intellia Tx** Invetech Invitria Invitrx IO Biosciences **Iovance IQVIA** ISSCR

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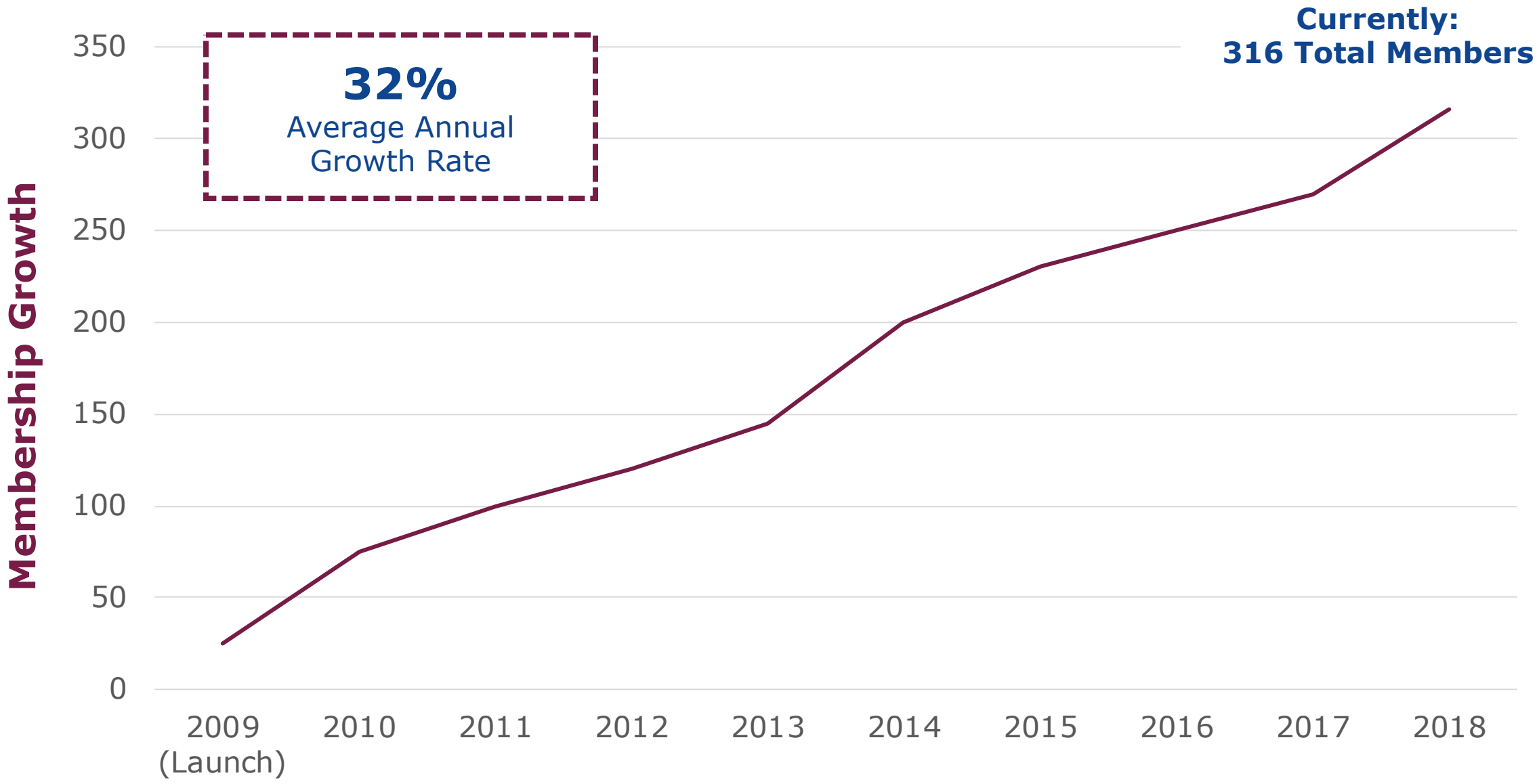
Johns Hopkins **Johnson & Johnson Kawasaki Heavy Industries** Key Biologics **Kiadis Pharma Krystal Biotech** LabConnect Lake Street Capital Markets LatticePoint Consulting Legend Biotech LogicBio Longeveron **Lonza Biologics** Ludwig Boltzmann Institute Lynch Biologics **Lysogene Magenta Tx** MaSTherCell **MaxCyte** Medeor TxBiotech MEDIPOST America **Medpace** MeiraGTx **Mesoblast Ltd** Michael J. Fox Foundation **MilliporeSigma MiMedx** Minerva Biotech Miromatrix Missouri Cures **MolMed** Monarch Biosciences MSK Cancer Center MTF **Mustang Bio** Myonexus Tx Navan Tech NCLC NDRI **Neuralstem** NexImmune **Nightstar Tx** NJII NMSS Nohla Tx Northwestern University Novadip Biosciences **Novartis / Avexis Novellus** Novitas Capital **Novo Nordisk** NSCF NSCI NYSCF Ophthotech Opsis Tx Orbit Biomedical Orbsen Tx **Orchard Tx** Organabio **Organovo** Orig3n **Orthocell Oxford BioMedica** Pancella PDC*line Pharma **Pfizer Pluristem Tx PolarityTE** Poseida Tx Precision Bio Promethera Bio Regenerative Patch Tech Regenerex **ReGenesys Regeneus** REGENXBIO REMEDI ReNeuron RepliCel Rexgenero **Rocket Pharma** RoosterBio Roslin Cell Therapies RxGen **Saint-Gobain SanBio** Sanford Health Sanford Stem Cell Center **Sangamo Tx / TxCell Sanofi / Bioverativ Sarepta** Sartorius Scinogy SCM LifeScience Semma Tx Sentien Biotech Seraxis **Sernova** Sigilon Skingenix SNBTS **Solid Bio Spark Tx** SSSCR STEL Technologies StemBioSys StemCyte Stop ALD Foundation Synpromics Tenaya TERMIS-Americas Terumo BCT Tessa Tx Texas Heart Institute **Thermo Fisher** Thrive Bioscience **TiGenix** TikoMed Tmunity Tx TrakCel Trizell Tulane University UC Irvine UCSD Stem Cell Program **Ultragenyx** UM Stem Cell Institute UMass Medical School Unicyte **uniQure** Unite 2 Fight Paralysis United Spinal Assn of VA **Universal Cells** Abramson Cancer Center **Vericel** VERIGRAFT ViaCyte VidaCel Videregen VINETI ViveBiotech Vivet Tx Voisin Consulting **Voyager Tx** WindMIL Tx World Courier Wuxi **Xintela** Yposkesi Zelluna

ARM Membership



Industry Overview

- 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

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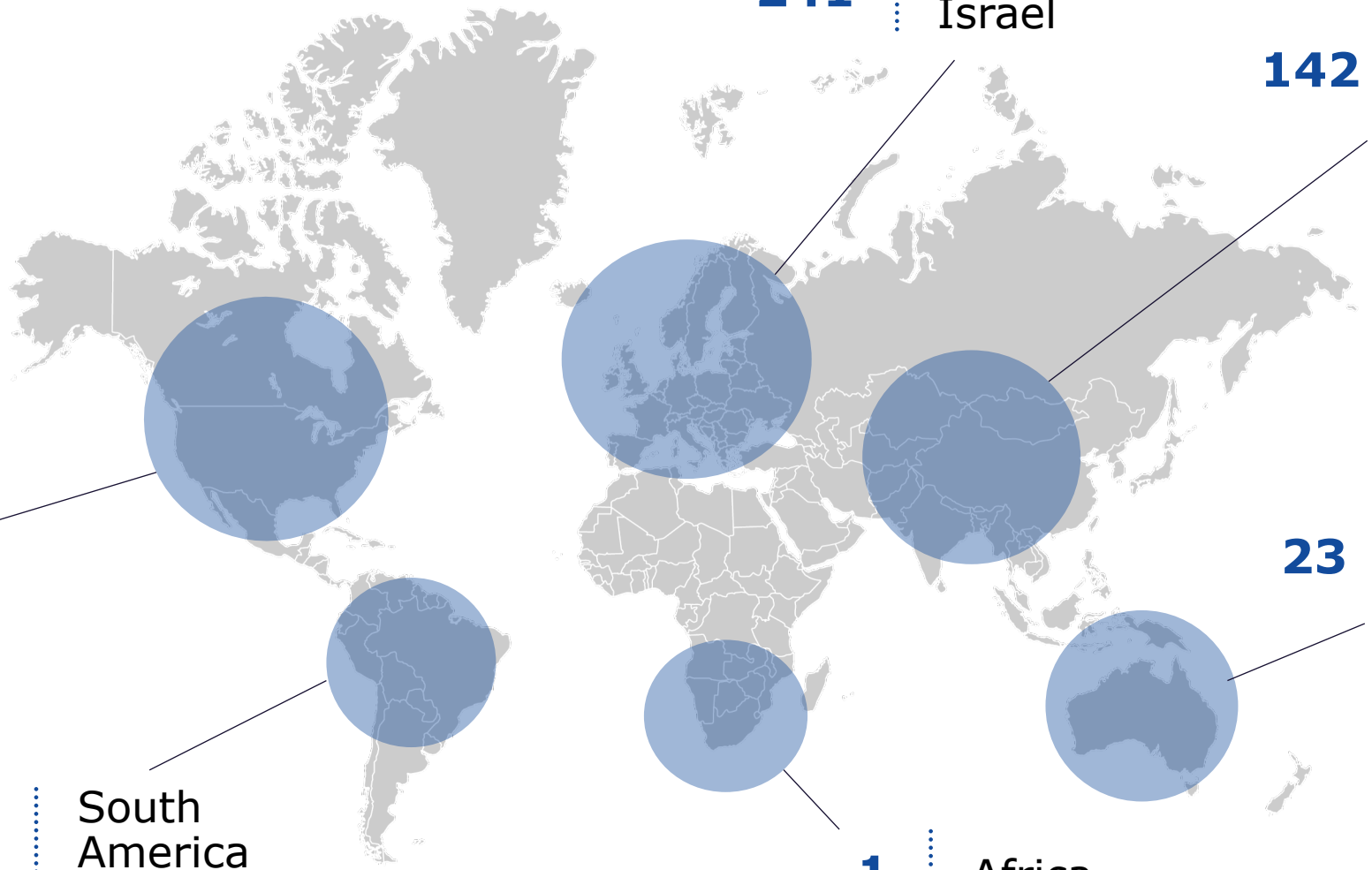
Current Global Sector Landscape

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



241 Europe & Israel

142 Asia

484 North America

23 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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- **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

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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 matric 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

Source data provided by: informa

Total Clinical Trials by Technology Type, EOY 2018

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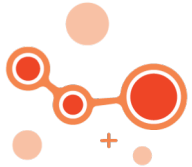
Gene Therapy

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

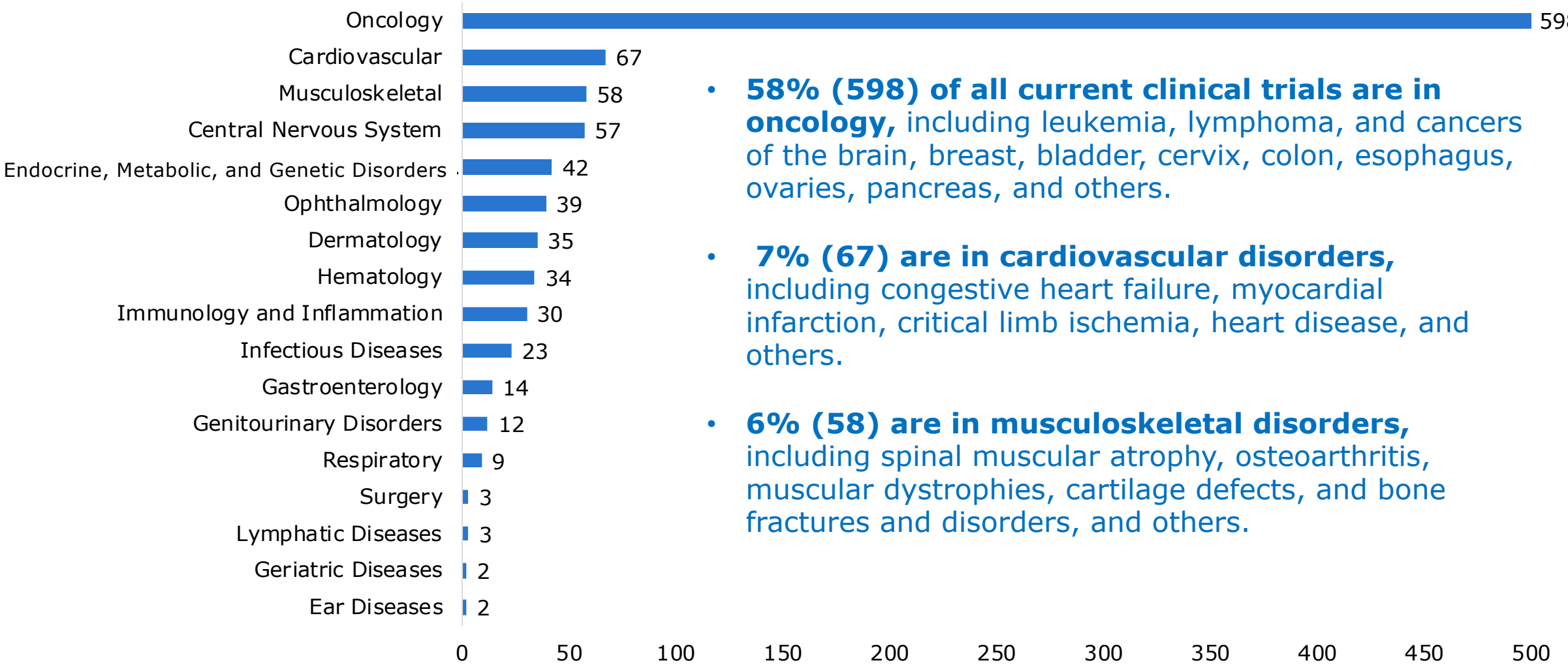
Total: 263
Phase I: 53
Phase II: 177
Phase III: 33

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

Patient Impact of Regenerative Medicine

59,575

Total Targeted Enrollment of Patients in Current Regenerative Medicine Clinical Trials Worldwide

9,533

Target Enrollment of Phase I Clinical Trials

29,069

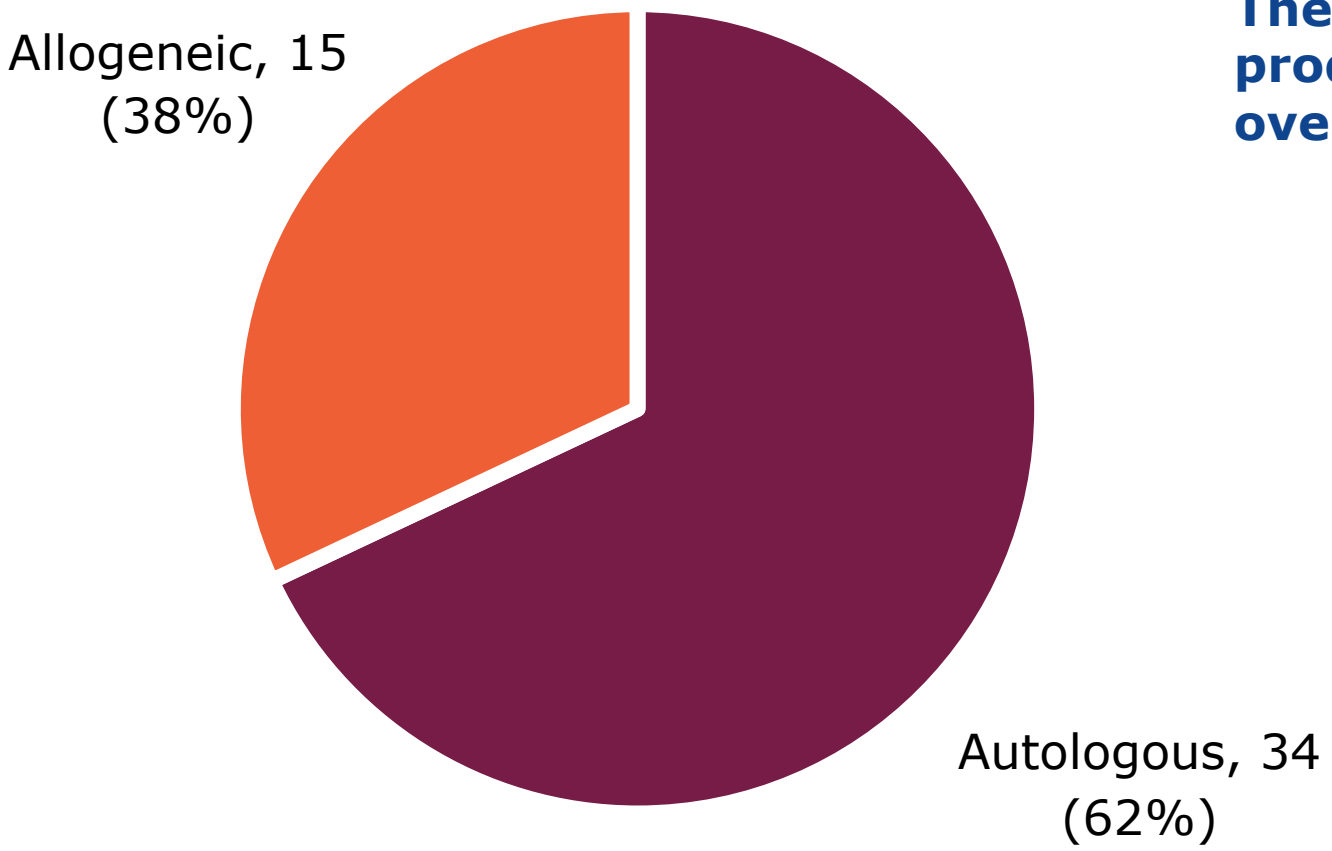
Target Enrollment of Phase II Clinical Trials

20,973

Target Enrollment of Phase III Clinical Trials

Source data provided by: informa

Allogeneic vs. Autologous Cell Therapies in Phase III Trials



The number of allogeneic cell-based product candidates is likely to increase over the next few years.

- Faster delivery to patients
- Easier to manufacture at scale
- More readily available in countries without the infrastructure to support autologous manufacturing
- Cost-effective

Patient Impact of Regenerative Medicine

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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%

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%

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

Select Anticipated Data Readouts: 2019

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Company	Product	Therapeutic Modality	Indication	Clinical Stage	Expected Reporting Date
GenSight Biologics	GS010	AAV-vector Gene Therapy	Leber Hereditary Optic Neuropathy	Ph III	Topline data Q1 2019
Asterias	AST-OPC1	Stem cell therapy	Severe spinal cord injury	Ph I/IIA	12 month results Q1 2019
Athersys	MultiStem	Cell therapy	Acute respiratory distress syndrome	Ph I/IIa exploratory	Q1 2019
Sentien Biotechnologies	SBI-101	MSC Device	Acute Kidney Injury	Ph I/II	Q1 2019
Audentes Tx	AT342	Gene therapy	Crigler-Najjar Syndrome	Ph I/II	Interim data Q1 2019
Axovant	AXO-AAV-GM2	Gene therapy	GM2 gangliosidosis	Ph I	Initial data Q1 2019
Fibrocell	FCX-007	Gene Therapy	Recessive Dystrophic Epidermolysis Bullosa	Ph I/II	Interim data Q1 2019
Caladrius	CLBS03	Cell therapy	Type 1 Diabetes	Ph II	Top-line data early 2019
Axovant	AXO-Lenti-PD	Gene therapy	Parkinson's disease	Ph II	March 2019
Mesoblast	MPC-25-IC	Allogeneic Mesenchymal Precursor Cell Therapy	Acute Myocardial Infarction	Ph II	1H 2019
Cytori	ECCI-50	Cell therapy	Male stress urinary incontinence	Ph III	1H 2019
Pfizer	PF-06939926	Gene therapy	Duchenne Muscular Dystrophy	Ph Ib	Early data 1H 2019
Hemostemix	ACP-01	Cell therapy	Critical limb ischemia	Ph II	Interim data mid-2019
Bone Tx	ALLOB	Cell therapy	Spinal Fusion	Ph IIA	Mid 2019
ReNeuron	hRPC product candidate	Cell therapy	Retinitis pigmentosa	Ph I/II	Top-line data mid-2019
Celyad	CYAD-01	CAR-T therapy	R/r AML/MDS	Ph I	Preliminary data mid-2019
Caladrius	CLBS14	Cell therapy	Coronary microvascular dysfunction	Ph II	Top-line data 2H 2019
Enochian	ENO-1001	Genetically modified cell therapy	HIV/AIDS	Ph I/II	Q4 2019
REGENXBIO	RGX-121	Gene therapy	MPS II	Ph I/II	2019
Homology Medicines	HMI-102	Gene therapy	Phenylketonuria	Pre-Ph I	Initial data 2019

Source: Company-provided or publicly-available information

Sector Financings

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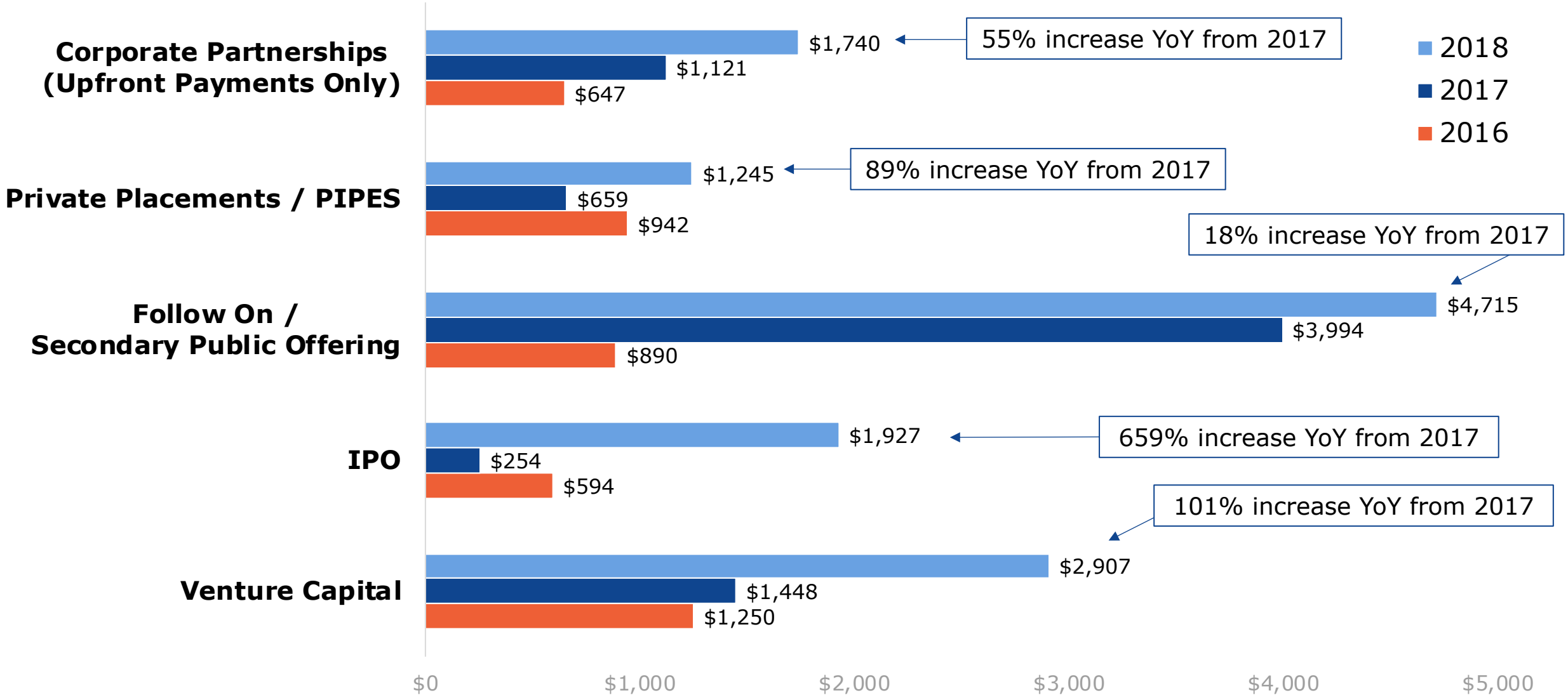
Total Global Financings: 2018

$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

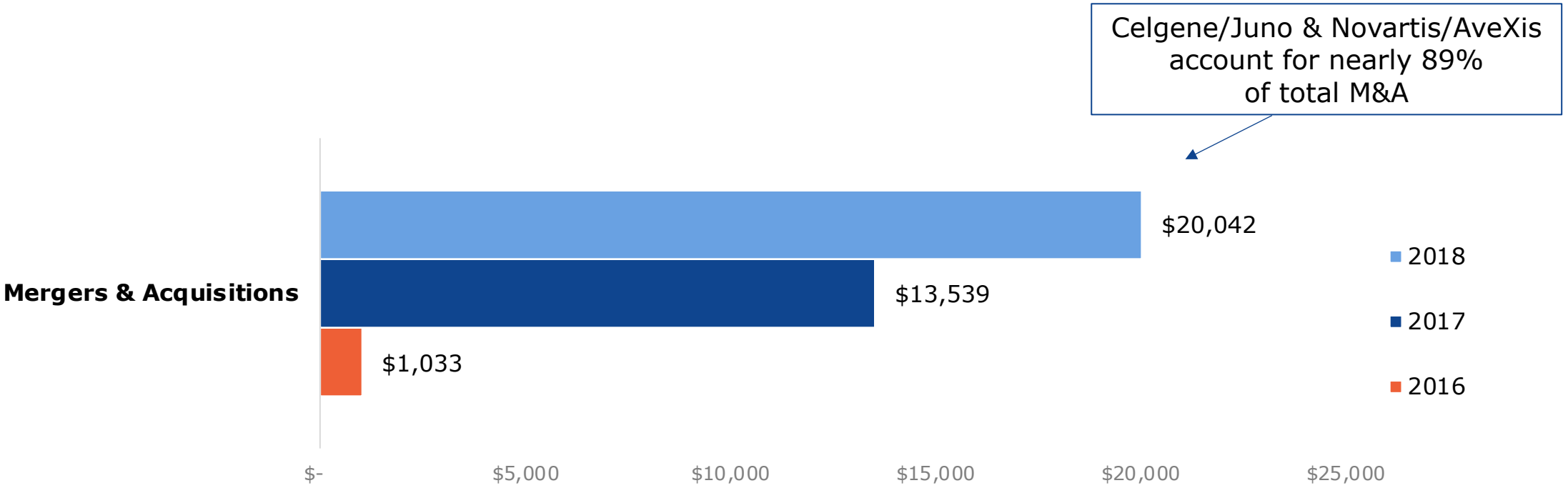
**both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies*

Total Financings by Type, by Year



Source data provided by: informa

Total M&A Transactions Values, By Year



Source data provided by: informa

Policy Environment

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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

Opportunities for Standardization

- Regulatory bodies are increasing focus on producing guidance for CMC issues
- International regulatory convergence on requirements for the research, development, and manufacturing of regenerative medicines & advanced therapies will improve patient access, decrease costs, allow safe & effective products to be product to market more efficiently

- The Standards Coordinating Body:
    - Coordinates and communicates about standards activities across the regenerative medicine community to accelerate standards advancement
    - Engages the broader community in the identification, prioritization, and advancement of potential standards to incorporate a range of perspectives and expertise
    - Educates the community about available standards and their benefits, standards development processes, and standards implementation

Market Access Landscape in 9 Countries

As of January 2019

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Kymriah ★

Yescarta ★

Alofisel ★ ✓

Imlygic ✓

Kymriah ✓

Luxturna ✓

Strimvelis ✓

Yescarta ✓

Zalmoxis ★ ✓

Holoclar ★

Imlygic ★ ✓

Kymriah ★ ✓

Strimvelis ★ ✓

Yescarta ★ ✓

Holoclar ★

Imlygic
Authorized, hospital only

Strimvelis ★ ✓

Zalmoxis ★ ✓

Imlygic ★ ✓

Imlygic ★ ✓

Kymriah ★ ✓

Luxturna ★ ✓

Yescarta ★ ✓

★ Kymriah
CADTH Assessment: Would be cost effective if price lowered

Yescarta
Undergoing CADTH assessment

Kymriah
Undergoing MSAC assessment

Kymriah
Expected to be covered nationally

★ *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!

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