Cell & Gene Therapy Sector Overview

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Alliance *for* Regenerative Medicine

Agenda

- ARM Overview
- Global Sector Overview
- Clinical Progress
- Anticipated Clinical Data Events
- Sector Financings
- Public Policy Overview

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About ARM

- **International advocacy organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
  - Cell and gene therapy, tissue engineering
- **350+ members**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
  - Across 25 countries
- **Priorities:**
  - Clear, predictable, and harmonized **regulatory** pathways
  - Enabling market access and value-based **reimbursement** policies
  - Addressing industrialization and **manufacturing** hurdles
  - Compile sector data, **educate** media and other stakeholders

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Current Global Sector Landscape

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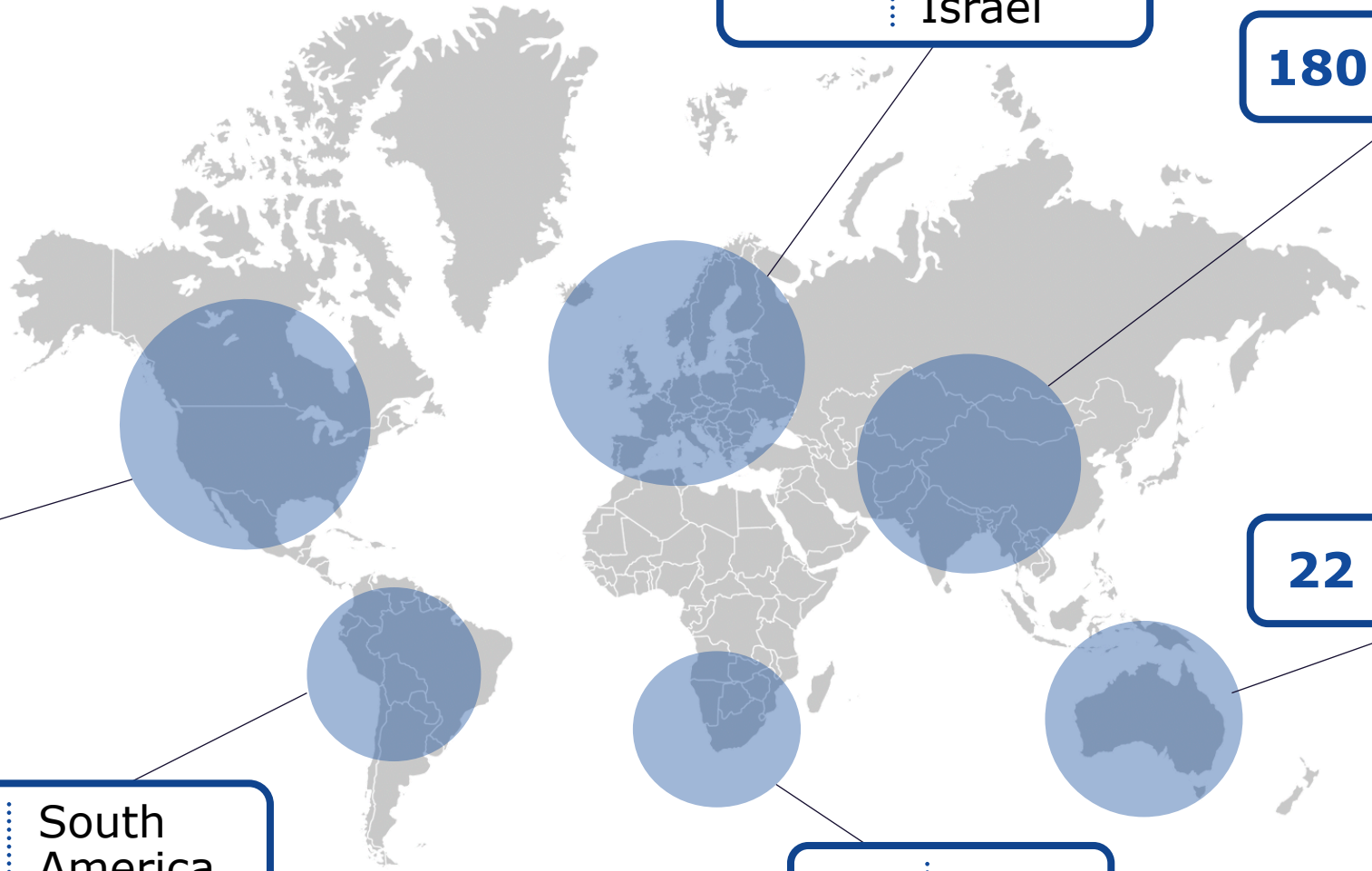
987+
Regenerative Medicine Companies Worldwide



237 Europe & Israel

180 Asia

534 North America

22 Oceania

Australia, New Zealand, Marshall Islands

13 South America

1 Africa

Global Sector Landscape

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24

RM Products Granted RMAT, PRIME, and/or SAKIGAKE Designations in 2019

1,066

Ongoing RM/AT Clinical Trials

$9.8B

Raised in Global Financings in 2019

2019 has been a significant year of growth for the regenerative medicine sector

Patient Impact of Recently Approved Products

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Therapy Name	Product Developer	Response
Zynteglo	bluebird bio	• **75%** of patients with TDT without β0/β0 genotype treated achieved transfusion independence
Zolgensma	AveXis, a Novartis company	• **93%** of SMA Type 1 patients treated were alive without permanent ventilation at 24 months post-treatment
LUXTURNA	Spark Therapeutics	• **93%** of patients treated showed an improvement of at least 1 light level from baseline
Yescarta	Kite Pharma, a Gilead company	• **58%** of patients with R/R B-Cell NHL treated experienced a complete response
Kymriah	Novartis	• **40%** of patients with R/R DLBCL treated experienced a complete response • **82%** of patients with R/R B-Cell ALL treated experienced complete remission or complete remission with incomplete hematologic recovery

- *60,000+ patients to be enrolled in RM clinical trials*
- *500,000+ patients treated with cell and gene therapies by 2030 in the US alone**

**MIT NEWDIGS estimate*

Select Anticipated Approvals in 2020

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Gene Therapy

Zolgensma (AveXis / Novartis)
- Spinal muscular atrophy type 1
- Filed for approval in EU and Japan mid-2019

ValRox (BioMarin)
- Severe hemophilia A
- Filed for approval in US and EU in December 2019

OTL-200 (Orchard Therapeutics)
- Metachromatic leukodystrophy
- Filed for approval in the EU in December 2019

GT-AADC (PTC Therapeutics)
- AADC deficiency
- Filed for approval in EU in January 2020

Zynteglo (bluebird bio)
- Beta thalassemia
- Filed for approval in US in January 2020

Tissue Engineering

RVT-802 (Enzyvant Therapeutics)
- Pediatric Congenital Athymia
- US filing accepted for review in June 2019

Cell Therapy

Remestemcel-L (Mesoblast)
- Acute graft versus host disease
- Initiated rolling BLA in US in May 2019

TEMCELL (Mesoblast / JCR Pharma)
- Epidermolysis bullosa
- Filed for market approval for additional indication in Japan in March 2019

Cell-Based Immuno-Oncology

liso-cel (Bristol-Myers Squibb)
- Relapsed or refractory large B cell lymphoma
- Filed for approval in the US in December 2019

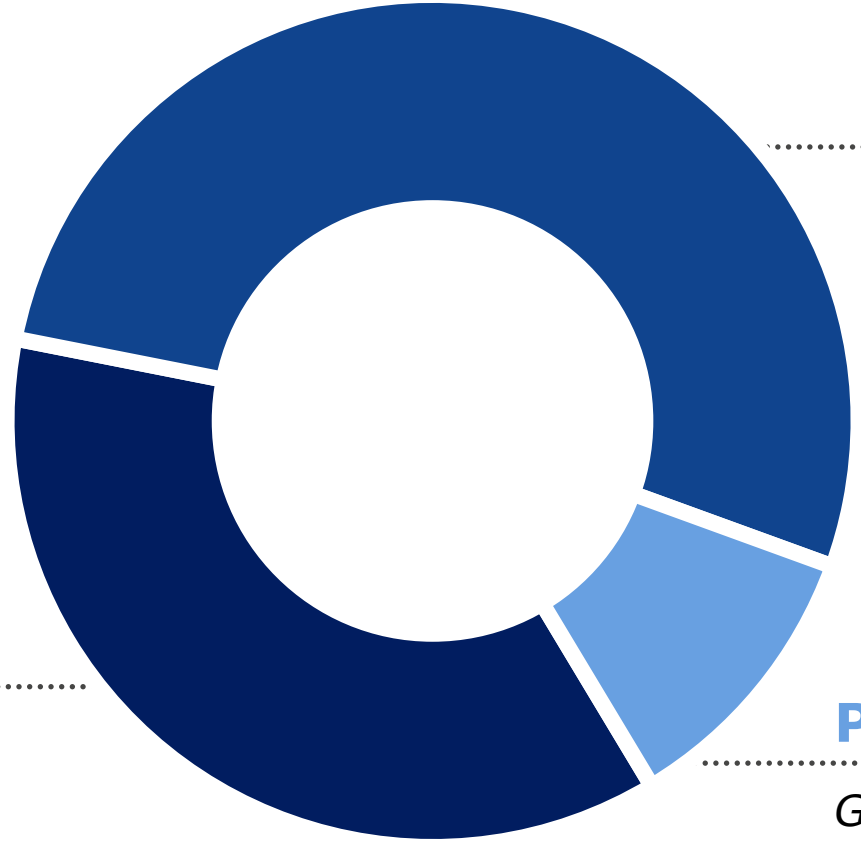
KTE-X19 (Kite Pharma / Gilead)
- Relapsed or refractory mantle cell lymphoma
- Filed for approval in the US in December 2019

Expecting to file in 2020:
- *Atara Bio – tab-cel*
- *Audentes Tx – AT132*
- *bluebird bio / BMS – ide-cel*
- *GenSight Bio – GS010*
- *Humacyte – Human Acellular Vessel*
- *Iovance – LN-145, lifileucel*
- *Mallinkrodt – Stratagraft*
- *Orchard – OTL-101, OTL-200 (US)*
- *PTC Tx – GT-AADC (US)*
- *Poseida – P-BMCA-101*

The Clinical Landscape for Regenerative Medicine in the US

572
Ongoing Regen Med Clinical Trials with US trial sites

Approximately ½ of ongoing regenerative medicine trials worldwide have a clinical trial site in the US



Phase 1: 210

Gene Therapy: 76
Gene-Modified Cell Therapy: 113
Cell Therapy: 17
Tissue Engineering: 4

Phase 2: 300

Gene Therapy: 138
Gene-Modified Cell Therapy: 101
Cell Therapy: 54
Tissue Engineering: 7

Phase 3: 62

Gene Therapy: 27
Gene-Modified Cell Therapy: 13
Cell Therapy: 12
Tissue Engineering: 10

The Clinical Landscape for Regenerative Medicine in the US

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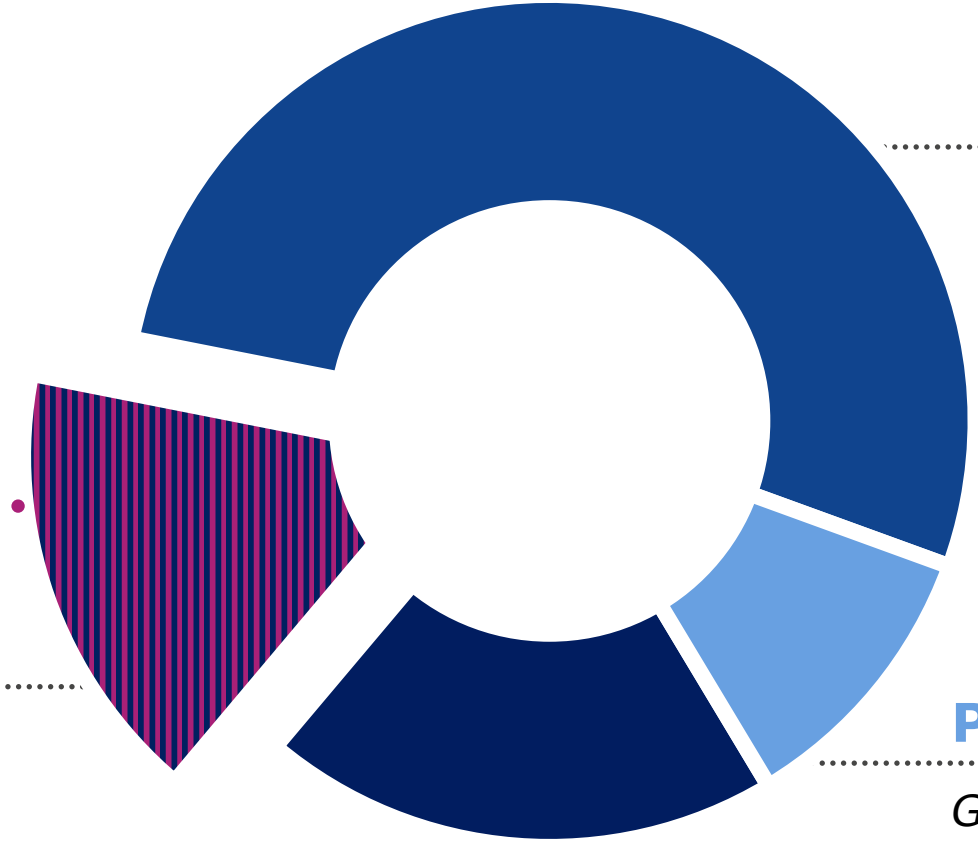
54%
of Phase 1 Trials are in gene-modified cell therapies



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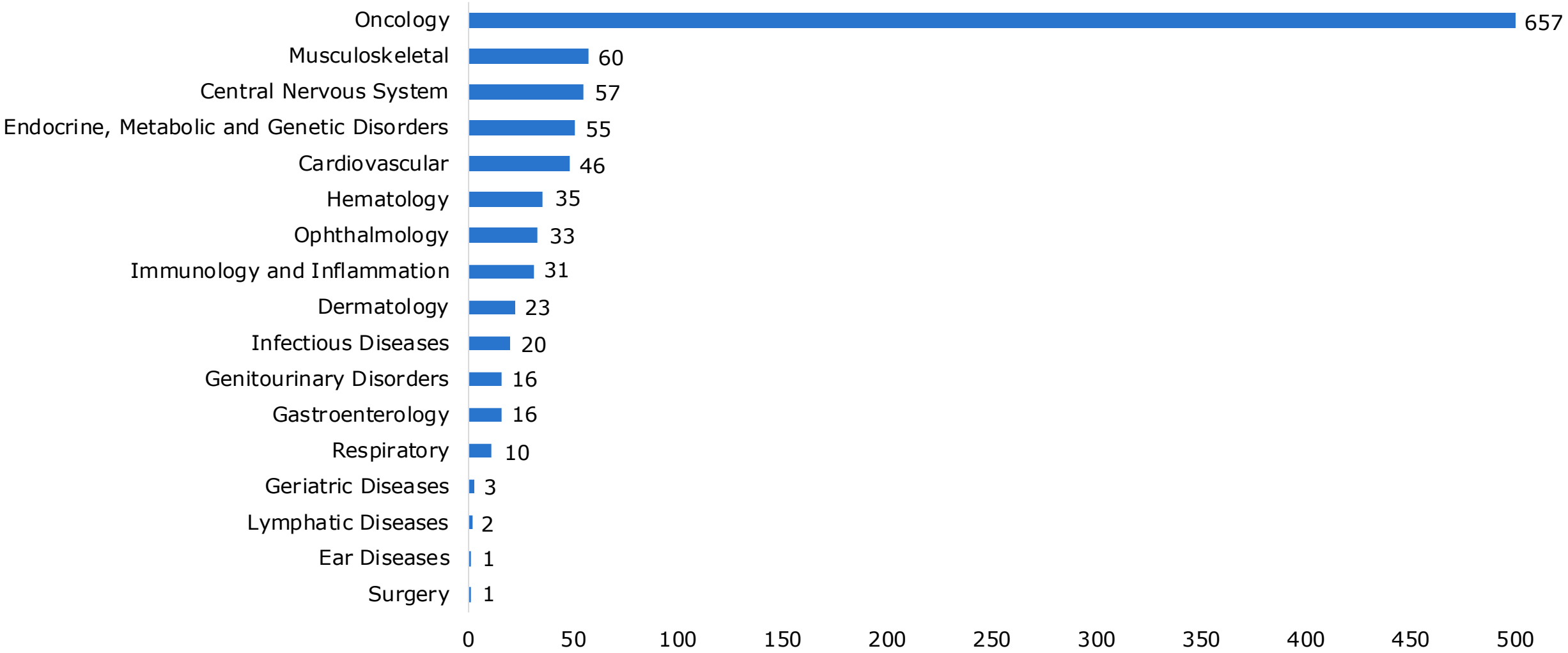
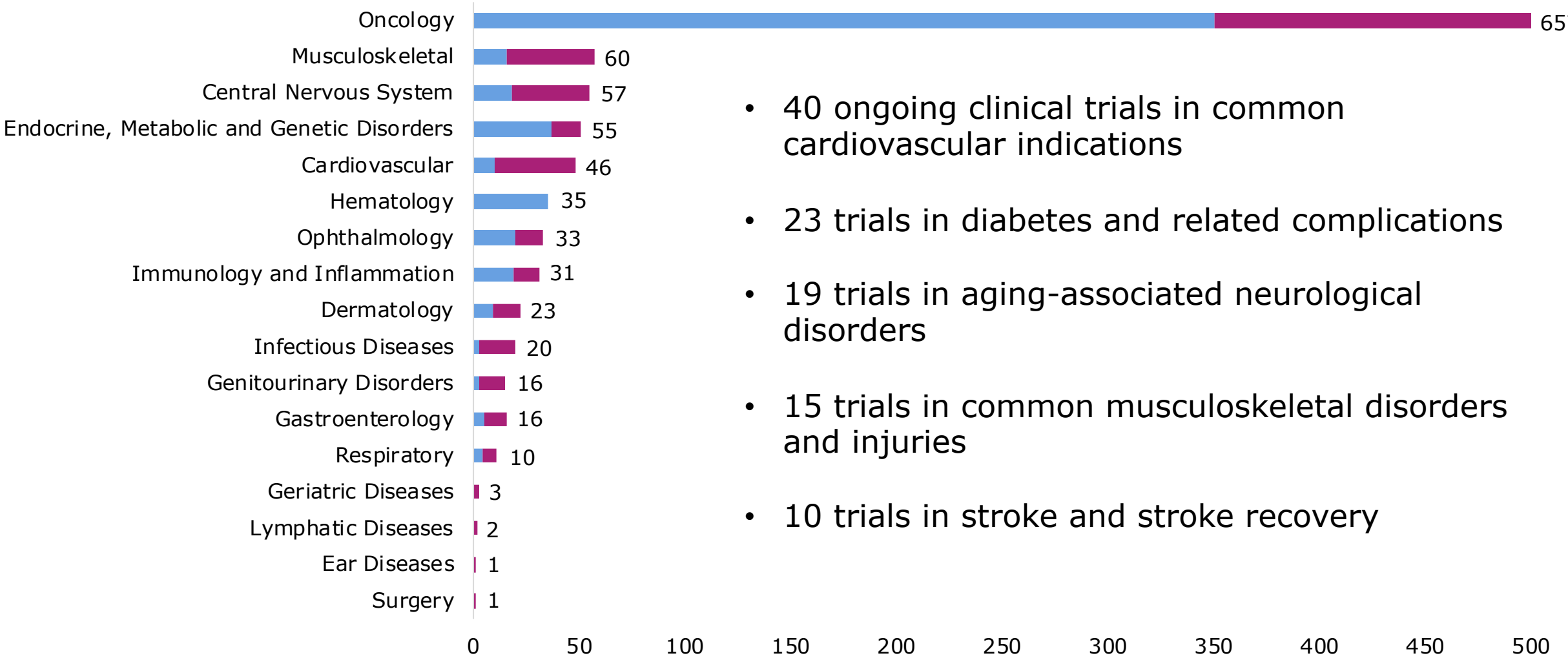
Clinical Trials Across Diverse Indications

Global Clinical Trials



Increasing Clinical Activity in Larger Indications Globally

More prevalent indications indicated in purple



- 40 ongoing clinical trials in common cardiovascular indications
- 23 trials in diabetes and related complications
- 19 trials in aging-associated neurological disorders
- 15 trials in common musculoskeletal disorders and injuries
- 10 trials in stroke and stroke recovery

Advances in Gene Therapy Delivery

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Researchers drove progress in gene therapy delivery methods:

BOSTON UNIVERSITY

BU researchers create new protocol to improve gene therapy tool production

OHIO STATE NEWS

A new gene therapy strategy, courtesy of Mother Nature

Scientists turn a natural cellular process into a drug-delivery system

NIH

NIH researchers create new viral vector for improved gene therapy in sickle cell disease

NEWS

Tiny capsules packed with gene-editing tools offer alternative to viral delivery of gene therapy

Johns Hopkins Researchers Advance Search For Safer, Easier Way to Deliver Vision-Saving Gene Therapy to The Retina

Scripps Research team finds that a nontoxic molecule can overcome barriers to delivering gene therapy into stem cells.

Non-viral delivery advancements:

- Japan approved Colletagene, a non-viral gene therapy to treat critical limb ischemia
- There are currently 57 ongoing gene therapy trials utilizing non-viral delivery methods

Companies are partnering to overcome challenges in gene therapy & gene-modified cell therapy manufacturing:

- Ziopharm Oncology and MD Anderson announced a new R&D agreement to expand TCR-T program
- SQZ Biotech and AskBio announced collaboration to overcome AAV immunogenicity

Expanding Manufacturing Capabilities

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Numerous companies invested in in-house manufacturing capabilities:

REUTERS

Pfizer, Novartis lead $2 billion spending spree on gene therapy production

Bloomberg

Kite Announces Plans for New State-of-the-Art Facility to Expand Cell Therapy Production Capabilities

BIOPHARMADIVE

BRIEF

Thermo Fisher opens $90M viral vector manufacturing plant in Massachusetts

Expanding Manufacturing Capabilities

Pre-market companies invested in manufacturing early:

AUDENTES

Audentes announced addition of cGMP plasmid manufacturing to existing large scale AAV operations

REGENXBIO™

REGENXBIO announced new manufacturing facility, to be operational in 2021

elevatebio

ElevateBio launched with $150M to provide centralized R&D and manufacturing capabilities to suite of CGT developers

PRECISION BIOSCIENCES

Precision BioSciences opened first in-house cGMP manufacturing facility dedicated to genome-edited allogeneic CAR-Ts in the US

Expanding Manufacturing Capabilities

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CMOs were attractive acquisition targets in 2019:

BioPharma-Reporter.com

Novartis acquires CellforCure to boost CAR-T manufacturing

FiercePharma

Hitachi gets EU cell manufacturing facilities with deal to buy Apceth Biopharma

GEN Genetic Engineering & Biotechnology News

Thermo Fisher to Acquire Brammer Bio for $1.7B

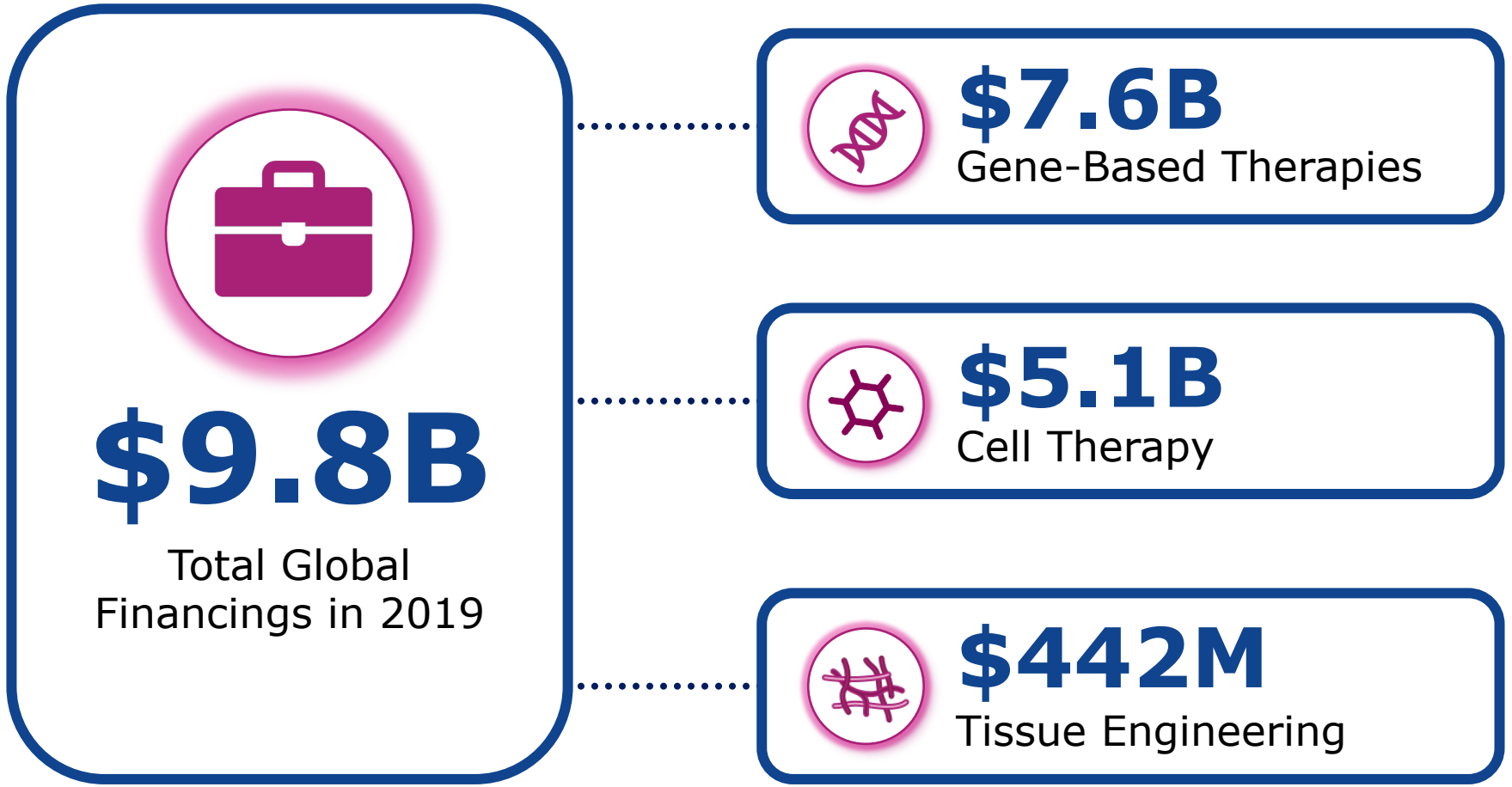
pharmaphorum

Catalent acquires gene therapy specialist Paragon for $1.2bn

Financing Trends

- ✓ *Total global financings in 2019 second highest ever for the sector*
- ✓ *Strong year for venture financing and corporate partnerships*
- ✓ *Large- and mid-cap pharma company M&A interest in cell & gene therapy*
- ✓ *European companies had a strong year for financings, on par with 2018*

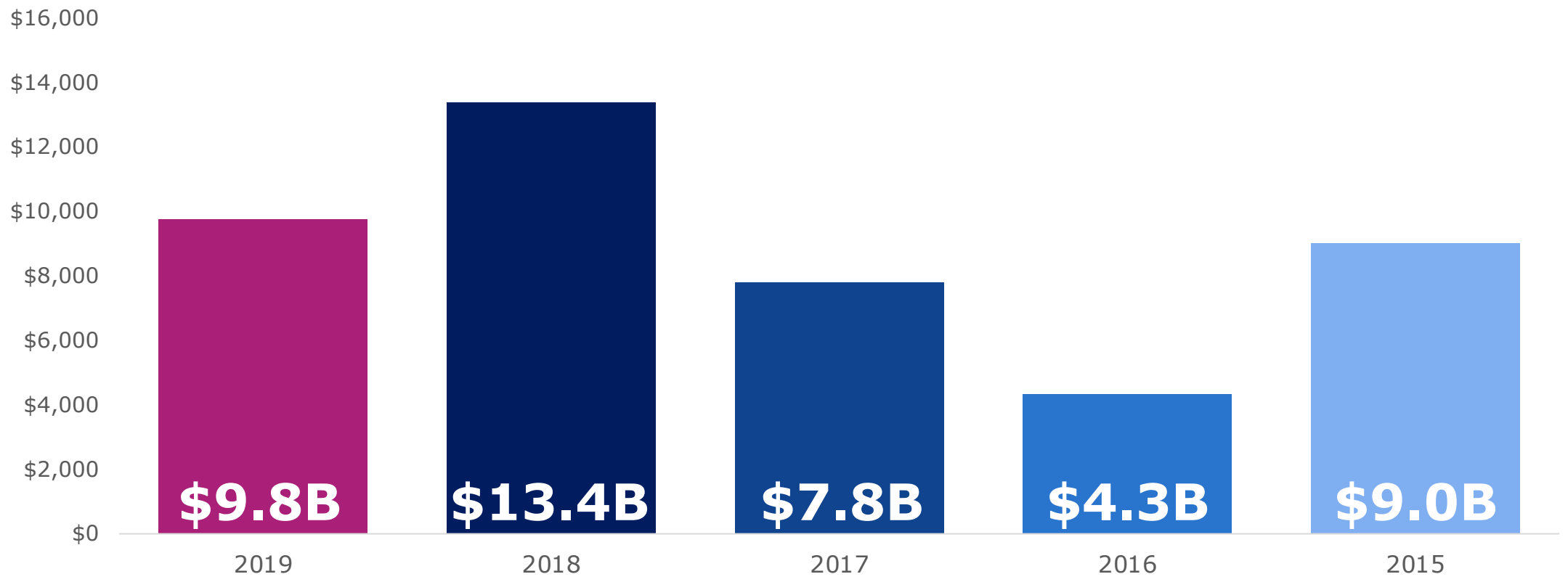
Total Global Financings 2019



*both Gene-Based Therapies & Cell Therapy categories include financings from companies active in developing gene-modified cell therapies – therefore, total financings does not equal the sum of each technology category

Source data provided by: informa

Total Global Financings by Year

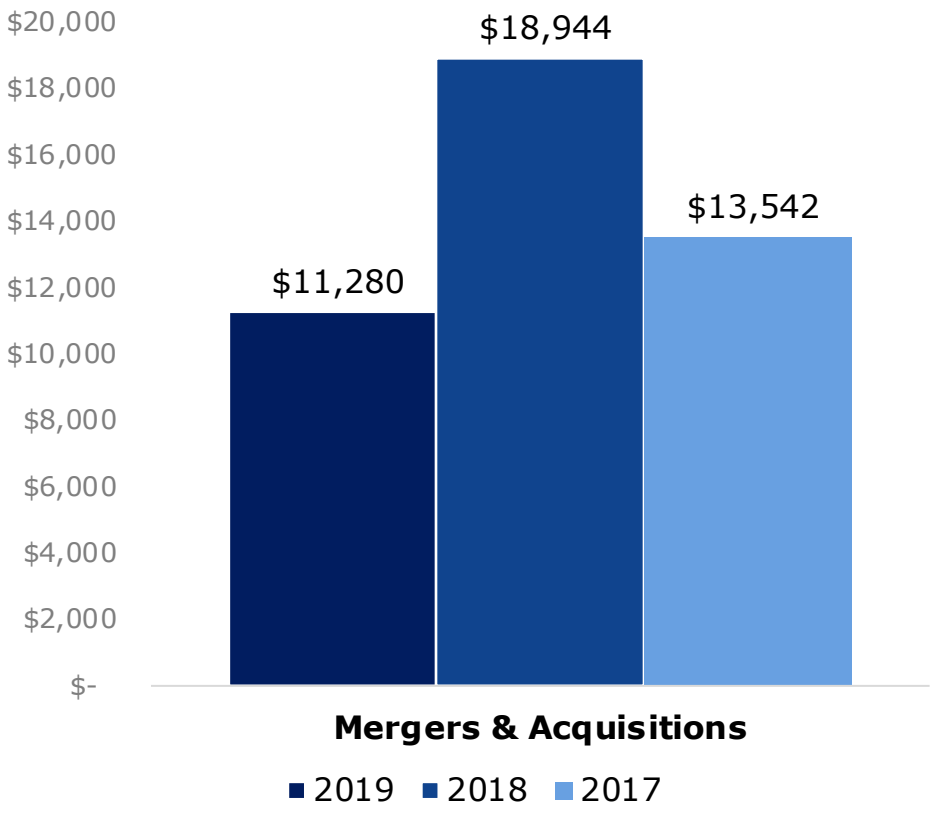


2019 surpassed 2015 in total global financings, making it the second highest year for financings ever

Source data provided by: informa

***M&A not included*

M&A Activity Reflects Growing Interest in Cell & Gene Therapy



Large and mid-cap pharma/bio acquisitions in the sector:

- Astellas acquires Audentes Tx for $3B*
- Roche acquires Spark Tx for $4.8B
- Vertex acquires Semma for $950M
- Biogen acquires Nightstar Tx for $877M
- Bayer acquires remaining stake in BlueRock Tx for $240M

**Not included in 2019 figure; deal closed in Q1 2020 and will be included in 2020 figures*

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:

- Two CMC specific guidances for cell and gene therapies released January 2020
- Disease-specific guidances on hemophilia, rare diseases, retinal disorders, January 2020
- Gene therapy "sameness" draft guidance released January 2020
- Supporting the Future of Rare Disease Product Development Public Meeting, February 2020

Positive Market Access Developments

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❑ CMS National CAR-T Coverage Decision

- Medicare coverage for all FDA-approved products

❑ FY 2020 Inpatient Prospective Payment System Rule

- Gathering data for potential CAR-T DRG

❑ Congressional CAR-T letter to CMS

❑ U.S. Senate VBP Provision; House VBP Bill

Sector Challenges

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❑ Reimbursement Models

- Public Payer: Regulatory/Legislative Roadblocks
- Commercial: One-offs
- CAR-T: Reimbursement inadequate/impact on patient access

❑ FDA

- CGT Reviewers

❑ Manufacturing

- Manpower
- Scale-up

CAR-Ts

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❑ Current Challenges

- Current reimbursement inadequate
- Add-on payment set to expire in 2020
- Patient access

❑ Crystal Ball Future

- More "traditional" CAR-Ts
- Local site manufacturing
- Off-the-shelf / allogeneic therapies
  - Cellectis, Precision, Celyad entered the clinic in 2019 with gene-edited allogeneic CAR-Ts
  - Increased preclinical activity and some clinical activity (Fate Tx) in allogeneic CAR-Ts utilizing iPSCs
- Increasing interest in CAR-Ts outside of oncology
  - Cartesian initiated clinical trial of their CAR-T for Generalized myasthenia gravis (autoimmune disorder)
  - Sangamo has received approval from the UK to initiate a trial of their CAR-Treg product to prevent immune rejection following kidney transplant

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Looking Forward: 2020+

The Outlook for 2020

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Clinical Data Readouts
Numerous high-profile data readouts expected in 2020

Hospital Exemption
Additional focus on safety & efficacy for point-of-care administration

Product Approvals
Several anticipated product approvals; gene therapies likely to double within 1-2 years

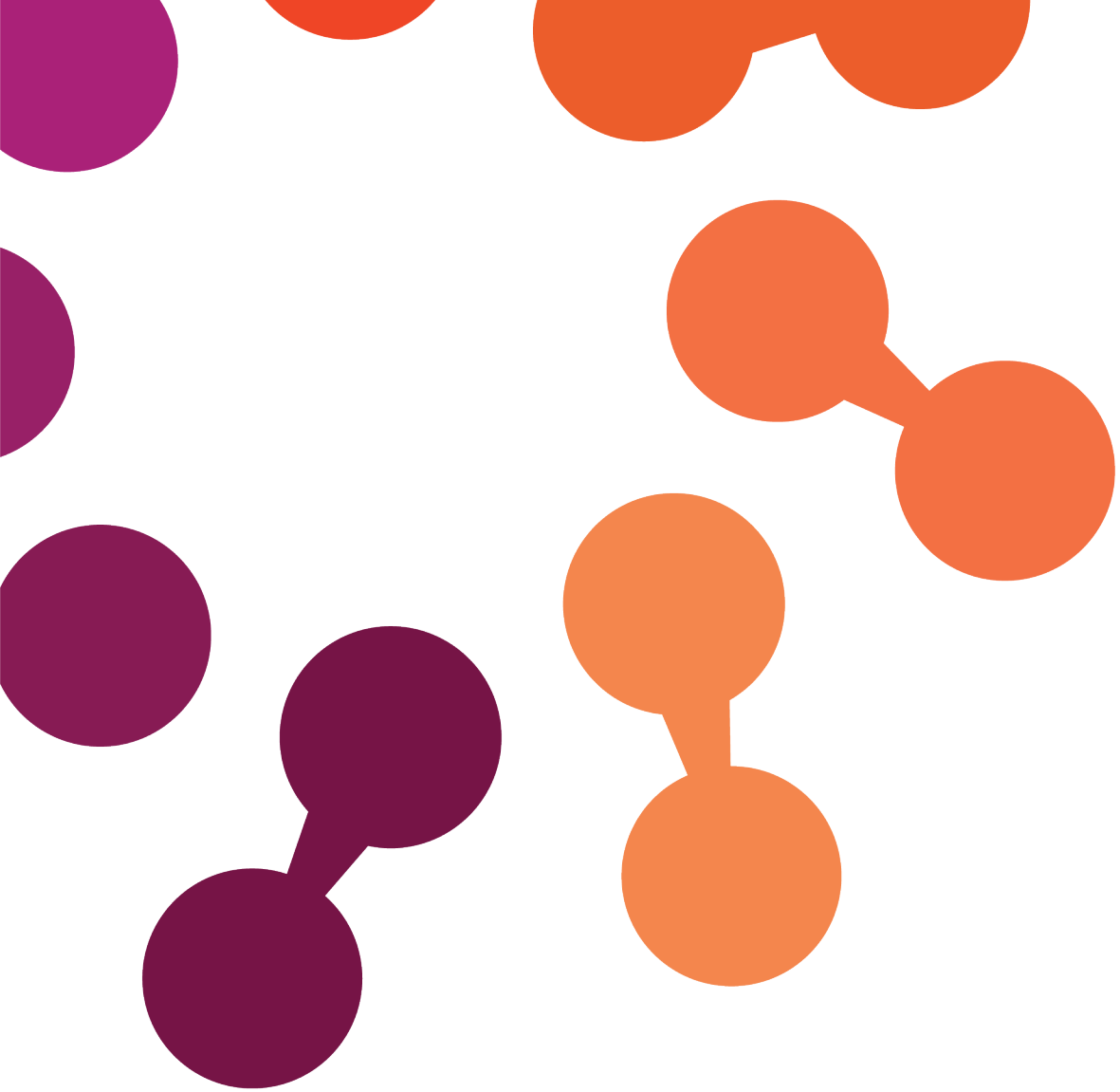
Stem Cell Clinics
Additional enforcement actions to be taken against 'rogue' stem cell clinics

Sector Financing
Strong demand for financing; IPO market constrained by US elections; indications generally strong

Drug Pricing
Moderate solution with increased emphasis on value in the RM sector

Gene Therapy Advances
Continued improvements in gene therapy delivery & manufacturing

Regulatory Environment
Continued support for the sector, with additional RMAT / PRIME designations expected



Thank You