Alliance *for* Regenerative Medicine

REGENERATIVE MEDICINE & RARE DISEASE 2019

Global Sector Report

Alliance for Regenerative Medicine

The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field.

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WHAT IS A RARE DISEASE?

A rare disease typically affects fewer than five in 10,000 people worldwide. Despite the rarity of each disease individually, when considered collectively, rare diseases affect a significant population – there are roughly 30 million people in the US and more than 300 million people worldwide living with a rare disease. There are nearly 7,000 different rare diseases currently identified, while only about 5% have an FDA-approved treatment. In addition, these diseases are often debilitating and potentially fatal; about 30% of children with a rare disease will die before their fifth birthday. Approximately 80% of rare diseases have identified genetic origins.

Significant progress in the fields of gene and cell therapy have opened up the possibility of durably treating and potentially curing many rare diseases, with particular progress in monogenetic diseases, which are caused by a defect in a single gene. The premise behind many of these therapies is relatively straightforward: patients with a rare disease gene are producing too much of, not enough of, or a diseased version of a particular protein or chemical, and the therapy is intended to add in or replace the proper version of that gene. In other cases, the therapy may provide or replace diseased or misfunctioning cells, tissues, or other structures.

Current therapeutic approaches include:

- Gene therapy, in which a delivery vehicle (often an engineered virus) will deliver a corrected or therapeutic version of a gene, or will silence the diseased gene in a patient's cells.
- Gene editing, a technique by which DNA is inserted, replaced, removed, or modified at particular locations in the human genome for therapeutic benefit.
- Gene-modified and cell-based immuno-oncology (IO), a technique used in many therapies being developed to treat rare cancers, by which specialized immune cells (which may be genetically modified to enhance their function) are administered to the patient to detect and kill cancerous cells.
- Cell therapy, involving the administration of viable, often purified cells into a patient's body to grow, replace, or repair damaged cells or tissue to provide a therapeutic benefit.
- Tissue engineering, an approach utilizing a combination of scaffolds, cells, and/or biologically active molecules to restore, maintain, improve, or replace tissues or organs affected by the disease.

REGENERATIVE MEDICINE & RARE DISEASE

There are an estimated **300 million patients** suffering from rare diseases worldwide.

There are currently **647 ongoing clinical trials** utilizing regenerative medicines to treat rare diseses.

There are more than **400 companies worldwide** active in developing regenerative medicines and advanced therapies for rare diseases.

Companies developing regenerative medicines for rare diseases raised more than **$6 billion in total financings** globally in 2019.

CLINICAL TRIALS IN RARE DISEASE

647 Clinical Trials in Rare Disease
Underway Worldwide by the End of 2019

Ph 1: 252 | Ph 2: 353 | Ph 3: 42

Clinical Trials by RM/AT Technology:

GENE THERAPY

Total: 220
Ph 1: 62
Ph 2: 134
Ph 3: 24

GENE-MODIFIED & CELL-BASED IO

Total: 351
Ph 1: 174
Ph 2: 168
Ph 3: 9

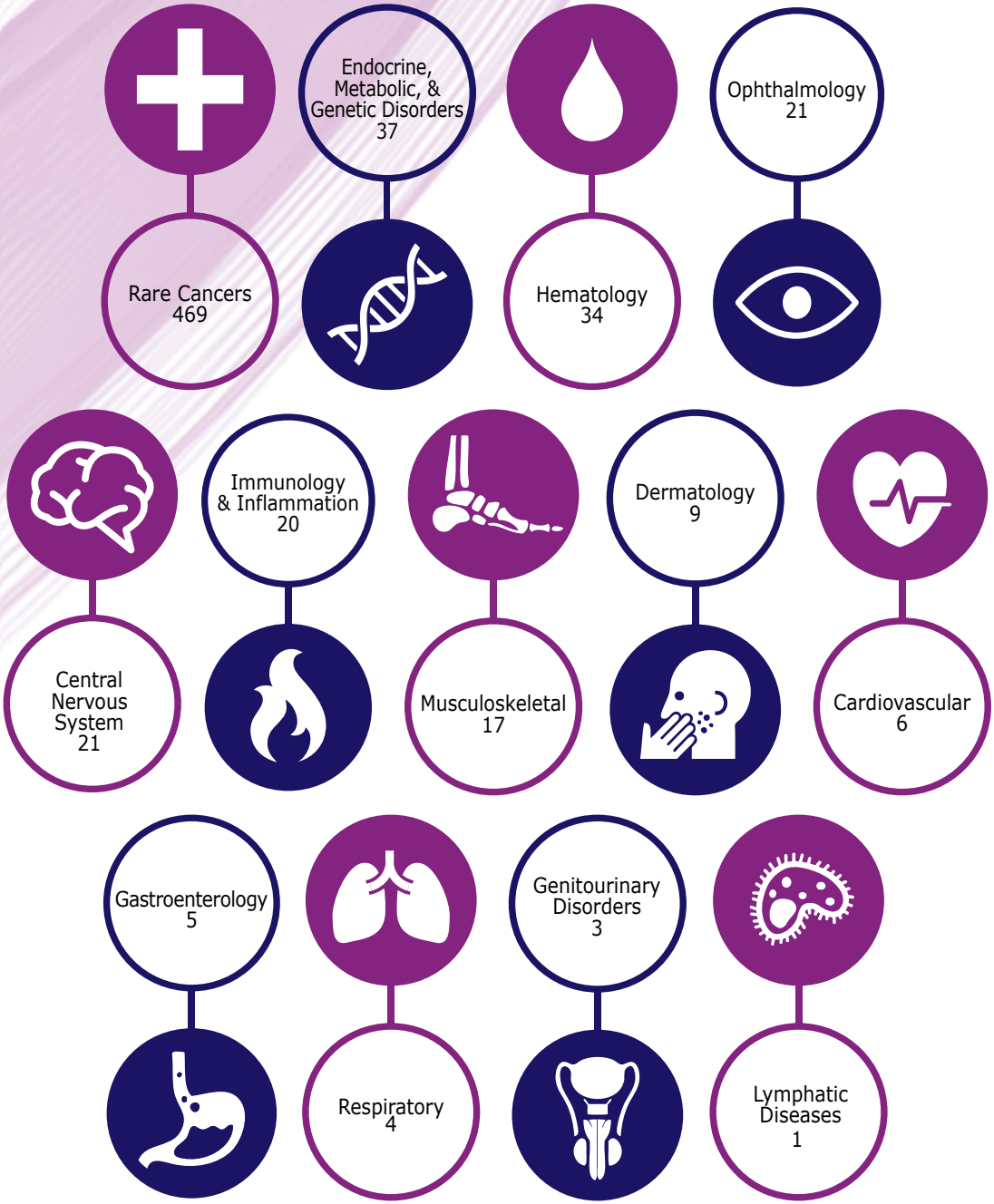
CELL THERAPY

Total: 70
Ph 1: 14
Ph 2: 49
Ph 3: 7

TISSUE ENGINEERING

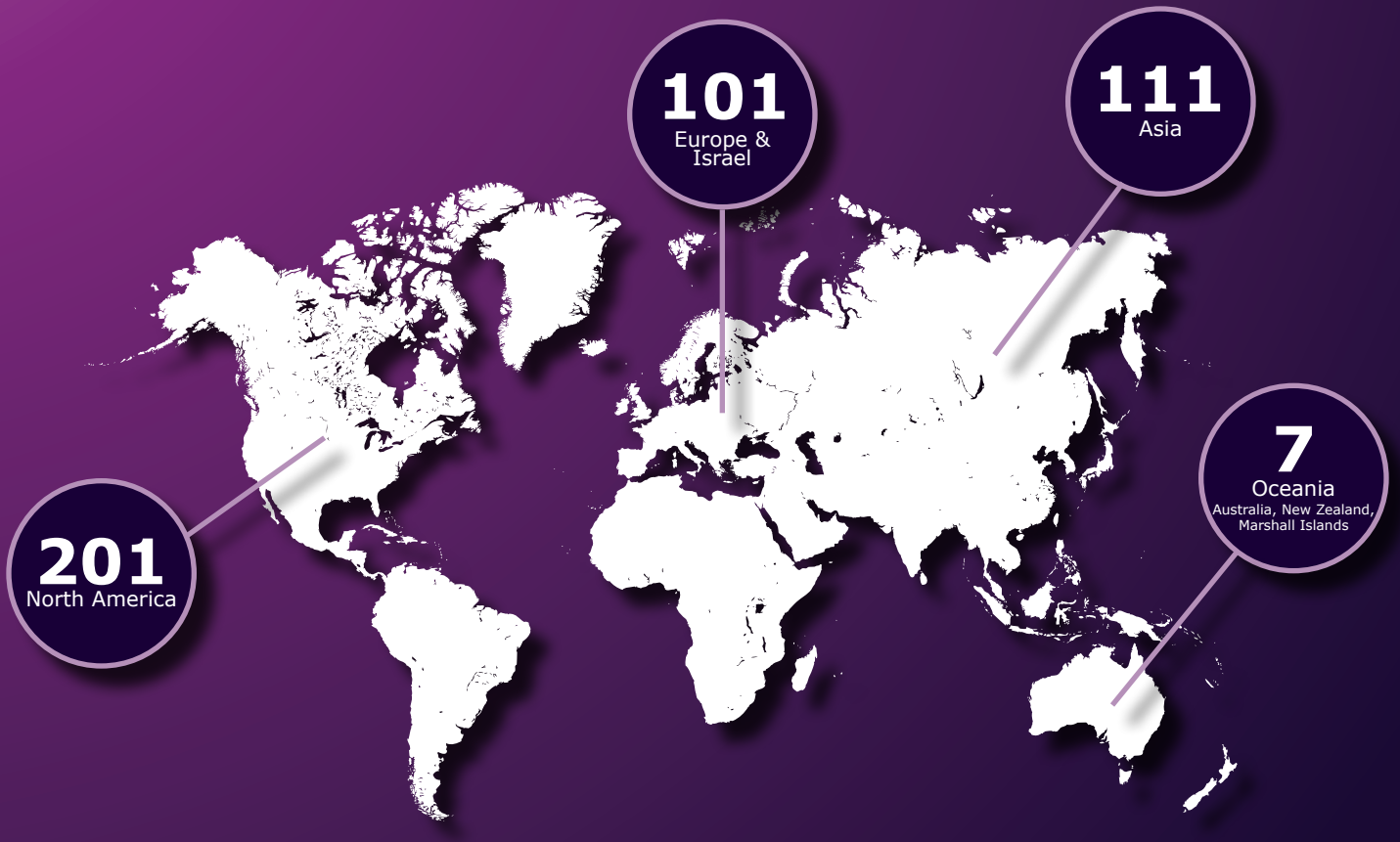
Total: 6
Ph 1: 2
Ph 2: 2
Ph 3: 2

CLINICAL TRIALS IN RARE DISEASE



RM/AT IN RARE DISEASE: GLOBAL LANDSCAPE

420+ **Regenerative medicine companies, including gene therapy, cell therapy, and tissue engineering companies, active in developing therapies for rare diseases worldwide**



Companies by Technology:

*Please note, individual companies may be active in more than one technology type

Gene Therapy: 286

Cell Therapy: 299

Tissue Engineering: 17

GLOBAL FINANCINGS IN RARE DISEASE

$6.4B

Total Global Regenerative Medicine Rare Disease Financings in 2019

$5.6B

Financings For Gene & Gene-Based Therapies for Rare Diseases in 2019

$3.5B

Financings for Cell Therapies for Rare Diseases in 2019

$2.9B

Finances for Companies Developing RM/AT Products for Rare Cancers in 2019

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

2019 was the second highest year on record for venture financing for rare disease in the regenerative medicine sector, raising $1.5B+

Examples of Rare Disease Financings in 2019:

Public Financings

- CRISPR Tx raises **$274M** in follow-on public offering – November 19
- uniQure raises **$225M** in follow-on public offering – September 4
- Sangamo Tx raises **$145M** in follow-on public offering – April 8
- AVROBIO raises **$138M** in follow-on public offering – July 19
- Orchard Tx raises **$128M** in follow-on public offering – June 10
- Homology raises **$125M** in follow-on public offering – April 12
- Abeona Tx raises **$104M** in follow-on public offering – December 24

Venture Financings

- Maze Tx launches with initial investment of **$191M** – February 28
- Beam Tx secures **$135M** in Series B – March 6
- Passage Bio raises **$115M** in Series A – February 14
- Passage Bio raises **$110M** in Series B – September 4
- Encoded Tx raises **$104M** in Series C – June 26

Corporate Partnerships
Upfront Payments Only

- Vertex & CRISPR Tx expand agreement to develop therapies for muscular dystrophies with **$175M** upfront – June 6
- Voyager Tx & Neurocrine Bio sign **$115M** upfront agreement to develop & commercialize gene therapies for neurodegenerative disorders, including Friedrich's Ataxia – January 29
- MeiraGTx and Jannsen sign **$100M** upfront agreement to develop gene therapies for inherited retinal diseases – January 31

RM/AT PRODUCT APPROVALS IN RARE DISEASE

ZOLGENSMA (AveXis / Novartis)

Approved in the US for the treatment of spinal muscular atrophy (SMA) – May 24, 2019

In March 2019, AveXis / Novartis reported that, of 21 patients enrolled in the STR1VE Phase 3 clinical trial of Zolgensma, 19 were alive and did not require permanent ventilator support. Without treatment, approximately 90% of SMA Type 1 patients will die by the age of 2.

ZYNTEGLO (bluebird bio)

Approved in the EU for the treatment of transfusion-dependent beta thalassemia (TDT) – June 3, 2019

In June 2019, bluebird bio reported that in the Phase 1/2 Northstar study of Zynteglo, 8 of 10 (80%) patients with beta thalassemia who do not have a β0/β0 genotype achieved transfusion independence. The patients continued to maintain transfusion independence until the data cut off, a duration of 21–56 months.

In addition, Kite / Gilead's CAR-T therapy **Yescarta** (first approved in the US in October 2017) was approved in Canada to treat pediatric patients with acute lymphoblastic leukemia and adult patients with diffuse large B-cell lymphoma in February 2019. Novartis's CAR-T therapy **Kymriah** (first approved in the US in August 2017) was approved in Japan to treat pediatric patients with acute lymphoblastic leukemia in March 2019.

ANTICIPATED NEAR-TERM APPROVALS

United States

BioMarin: ValRox
Gene therapy, hemophilia A
Submitted BLA in December 2019

bluebird bio: Zynteglo
Gene therapy, beta thalassemia
Initiated rolling BLA in January 2020

Enzyvant: RVT-802
Tissue engineering, pediatric congenital athymia
FDA accepted rolling BLA in June 2019

Kite / Gilead: KTE-X19
CAR-T therapy, mantle cell lymphoma
Submitted BLA in December 2019

Mesoblast: Ryoncil
Cell therapy, acute graft vs. host disease
Completed rolling BLA in January 2020

European Union

AveXis / Novartis: Zolgensma
Gene therapy, spinal muscular atrophy
Submitted MAA mid-2019

BioMarin: ValRox
Gene therapy, hemophilia A
Submitted MAA in November 2019

Orchard Therapeutics: OTL-200
Gene therapy, metachromatic leukodystrophy
Submitted MAA in December 2019

PTC Therapeutics: GT-AADC
Gene therapy, AADC deficiency
Submitted MAA in January 2020

Japan

AveXis / Novartis: Zolgensma
Gene therapy, spinal muscular atrophy
Submitted MAA mid-2019

SPOTLIGHT: ZOLGENSMA & ZYNTEGLO

In 2019, the regenerative medicine sector experienced two major approvals in the rare disease space: AveXis / Novartis's Zolgensma (onasemnogene abeparvovec-xioi), an *in vivo* AAV gene therapy for the treatment of spinal muscular atrophy (SMA) type 1 in infants under the age of two, and bluebird bio's Zynteglo (autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene), an *ex vivo* lentiviral gene therapy for the treatment of transfusion-dependent beta thalassemia (TDT).

Each of these therapies is poised to provide a substantial positive impact to thousands of patients. Prior to 2016, there was no approved treatment for spinal muscular atrophy; over 90% of infants born with SMA Type 1, the most serious form of the disease, would die or need permanent breathing support before the age of 2. Treatment with Spinraza, approved in 2016, requires invasive regular injections to the spinal cord and can cost millions of dollars over the lifetime of the patient.

TDT can cause life-threatening anemia if it goes untreated. Regular chronic blood transfusions, resulting in iron build-up in the heart and other organs, can contribute to serious medical complications in many patients. In both of these cases, gene therapy represents the potential to provide a significant improvement in the standard of care.

The approval of these therapies, which have a high upfront cost but represent incredible value to patients and healthcare systems over the course of a patient's lifetime, has spurred a conversation regarding patient access. Current reimbursement systems are typically designed to provide chronic care, whereas gene therapies and other regenerative medicines have the potential to provide a durable and perhaps curative therapeutic effect following a single administration.

Both AveXis, a Novartis company, and bluebird bio are engaging with payers and other stakeholders to develop and implement innovative financing models better suited to these complex therapies. AveXis is currently working with payers to create 5-year outcomes-based arrangements and pay-over-time options. bluebird bio has announced that they plan to offer 5-year payment plans for Zynteglo as well, with payments benchmarked against positive health outcomes. These types of arrangements help to offset the perceived risk of these novel therapeutics and amortize the cost in accordance with their long-term value.

As the number of approved gene therapies grows, it imperative that stakeholders continue to convene to identify strategies to ensure patients can access these lifechanging therapies.

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- Commentary from experts in the field

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