Alliance *for* Regenerative Medicine

Regenerative Medicine & Inherited Blood Disorders

April 2019

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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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Regenerative Medicine & Inherited Blood Disorders

Inherited blood disorders are caused by genetic defects which affect the production or function of red blood cells, white blood cells, or platelets. While these disorders all affect fewer than five in 10,000 people worldwide and are thus categorized as rare diseases, more than 20 million people worldwide suffer from symptomatic inherited blood disorders. There are limited treatments available to patients, which means that often those with severe forms of these disorders can have difficulty functioning in their day-to-day lives and may experience serious or fatal medical complications.

Numerous regenerative medicine-based approaches, including gene-based therapies, to durably treat or perhaps even cure several kinds of inherited bleeding disorders are in the clinic now, with several in late-stage clinical trials.

Some of the most common inherited blood disorders include:

Hemophilia: Hemophilia is an inherited disorder that impairs the body's ability to make blood clots, causing those affected by the disorder to bleed longer after an injury. This disorder can also cause complications during surgery. The most prevalent types of hemophilia are hemophilia A, which occurs due to an insufficient amount of clotting factor VIII, and hemophilia B, which occurs due to a lack of clotting factor IX. An estimated 400,000 people worldwide live with hemophilia.[1]

Currently, hemophilia patients are treated with infusions to replace the missing clotting factors. These infusions may be administered only during bleeding episodes, or they may be needed regularly. In some cases, patients may develop an immune response to the clotting factors, which can complicate treatment. However, there are several regenerative medicine therapies in development with the potential to provide a durable, long-term treatment or perhaps even a cure for hemophilia. These products use gene therapies or gene editing technologies to address the underlying genetic defect that prevents the production of clotting factors.

Beta thalassemia: Beta thalassemia is a type of inherited disorder that reduces the production of hemoglobin, the iron-containing protein on red blood cells that allows them to carry blood throughout the body, leading to anemia. Depending on the severity of the disorder, affected patients may experience fatigue, weakness, shortness of breath, dizziness, or headaches; anemia may cause severe or life-threatening complications if left untreated. An estimated 288,000 people worldwide suffer from beta thalassemia.[2]

Beta thalassemia is currently often treated with blood transfusions to raise the hemoglobin levels in the blood. Over time, chronic blood transfusions can result in additional medical complications from iron overload, including heart disease, liver disease, and endocrine disorders. Bone marrow transplants are also an option, though they can result in life-threatening complications. Regenerative medicine therapies in development for beta thalassemia include gene therapies and gene editing technologies to restore hemoglobin production.

Sickle cell disease: Sickle cell disease is a collection of inherited blood disorders in which an abnormality in the hemoglobin can cause blood cells to become rigid and "sickle-shaped" rather than their typical round shape. This can lead to a number of health problems, including long-term pain, anemia, swelling of the extremities, increased susceptibility to bacterial infections, and stroke. Approximately 20 million people worldwide suffer from sickle cell disease.[3]

The standard of care for sickle cell disease currently varies widely from patient to patient. Children diagnosed with sickle cell disease are often prescribed daily penicillin to combat the effects of a weakened immune system. Certain drugs may help to reduce the frequency of vaso-occlusive crises, in which affected blood cells cut off regular blood supply to a part of the body, causing considerable pain and potential organ damage or death. Blood transfusions have been found helpful in increasing the number of regularly shaped red blood cells in the body. Regenerative medicine therapies currently in development for the treatment of sickle cell disease include gene therapies and gene editing technologies to address the genetic cause of abnormal hemoglobin production.

ARM members active in developing therapies for inherited blood disorders include:

- Abeona Therapeutics
- Angiocrine Bioscience
- BioMarin Pharmaceutical
- bluebird bio
- Casebia Therapeutics
- CRISPR Therapeutics
- CSL Behring
- Editas Medicine
- Gamida Cell
- Immusoft Corporation
- Orchard Therapeutics
- Pfizer
- Promethera Biosciences
- Poseida Therapeutics
- PROMETHERA Biosciences
- Rocket Pharmaceuticals
- Sangamo Therapeutics
- Sanofi Genzyme
- Sernova Corp
- Sigilon Therapeutics
- Spark Therapeutics
- Ultragenyx Pharmaceutical
- uniQure

1 "Fast Facts," National Hemophilia Foundation, https://www.hemophilia.org/About-Us/Fast-Facts
2 "Gene Therapy as a Curative Option for β-Thalassemia," New England Journal of Medicine, https://www.nejm.org/doi/abs/10.1056/NEJMe1802169
3 "Sickle Cell Disease," National Heart, Lung, and Blood Institute, NIH, https://www.nhlbi.nih.gov/health-topics/education-and-awareness/sickle-cell

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Regenerative Medicine & Inherited Blood Disorders

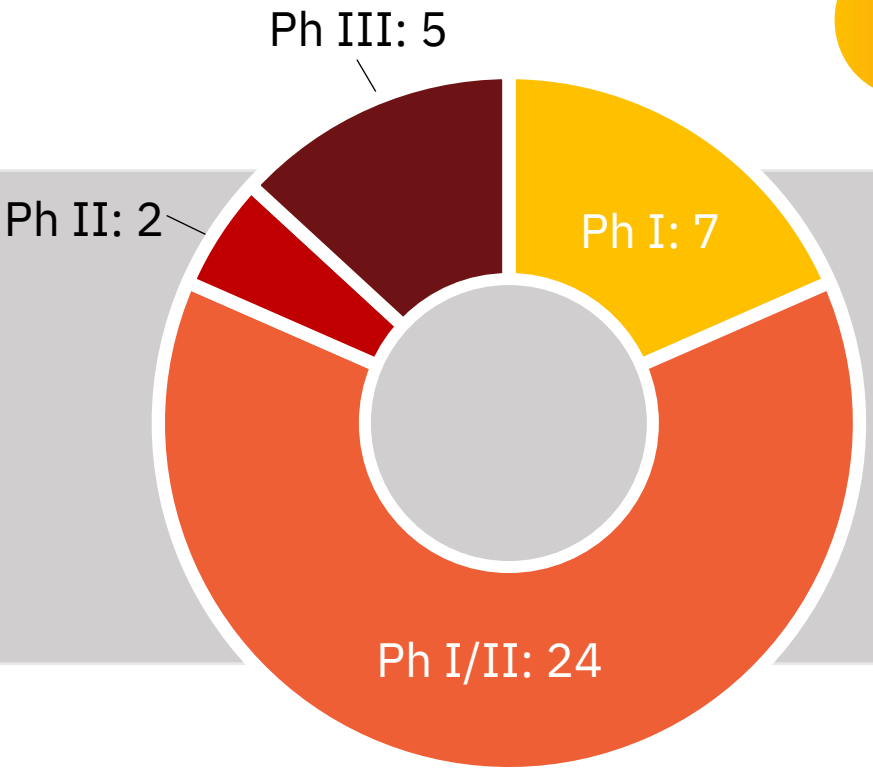
As of March 2019:

There are more than 20 million patients living with inherited blood disorders worldwide.

There are currently 50+ products in active development with 38 clinical trials ongoing, including five in Phase III.

There 31+ companies worldwide active in developing regenerative medicine therapies for inherited blood disorders, including 18 clinical-stage companies.

Clinical Trials in Inherited Blood Disorders



ARM currently tracks info from

38

clinical trials
in inherited blood disorders

All data and figures calculated through the end of March 2019.

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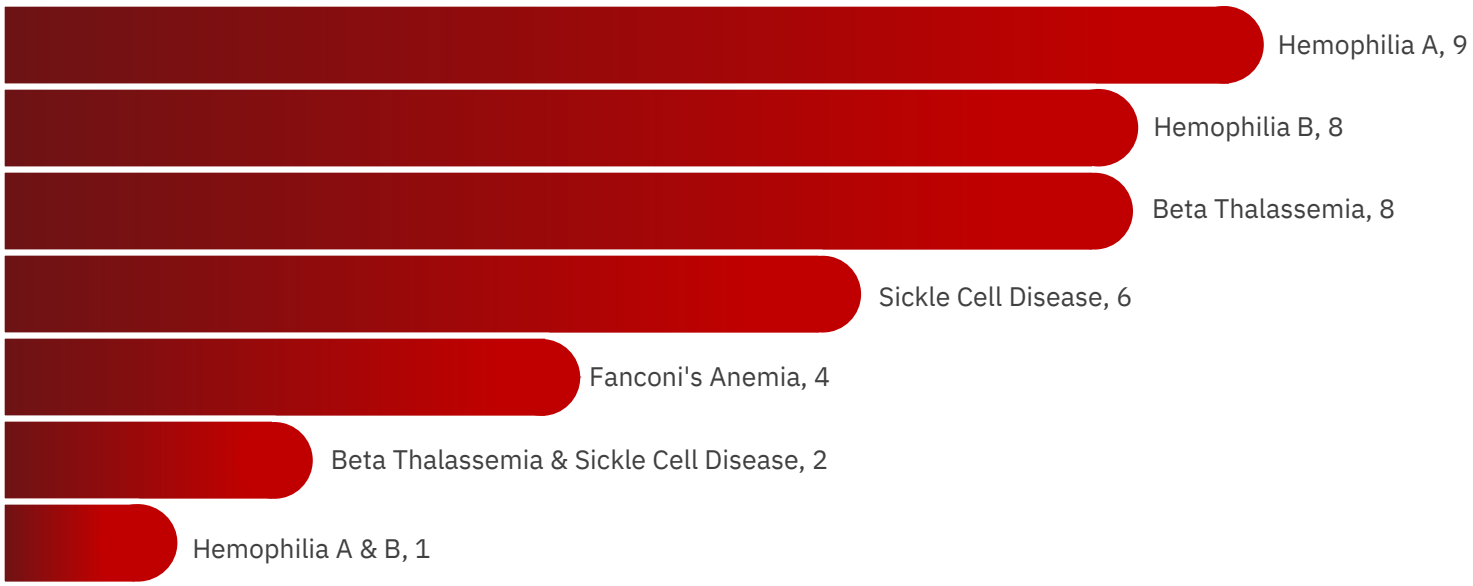
Clinical Trials by Indication & Technology Type

Clinical Trials by Indication



Clinical Trials by Technology

Gene Therapy
Total: 32

AAV Vectors:
Phase I: 3
Phase I/II: 4
Phase II: 1
Phase III: 2

Lentiviral Vectors:
Phase I: 5
Phase I/II: 8
Phase III: 2

Gene Editing
Total: 5

Zinc Finger Nuclease
Phase I: 1
Phase I/II: 2

CRISPR
Phase I/II: 2

Cell Therapy
Total: 1

Stem & Progenitor Cells
Phase I/II: 1

Gene therapy total does not include clinical trials using gene editing technologies.
All data and figures calculated through the end of March 2019.

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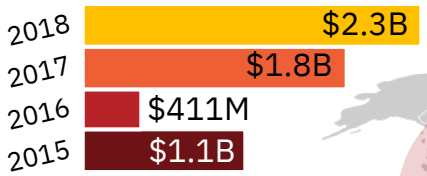
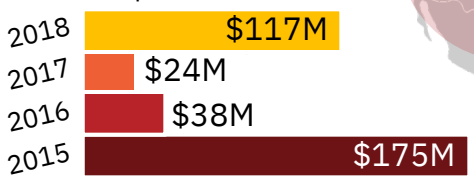
Companies & Financings in Inherited Blood Disorders

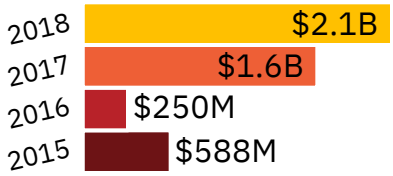
Total Financings

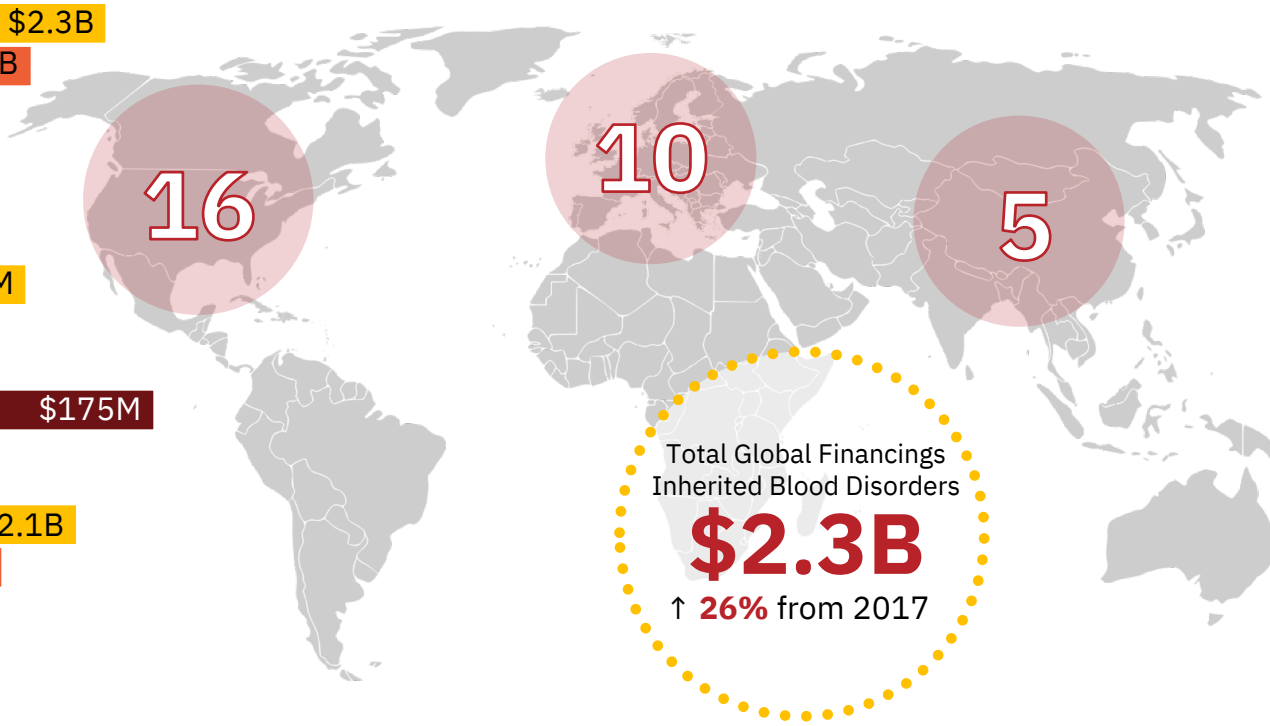


Venture Capital



Follow On Financings



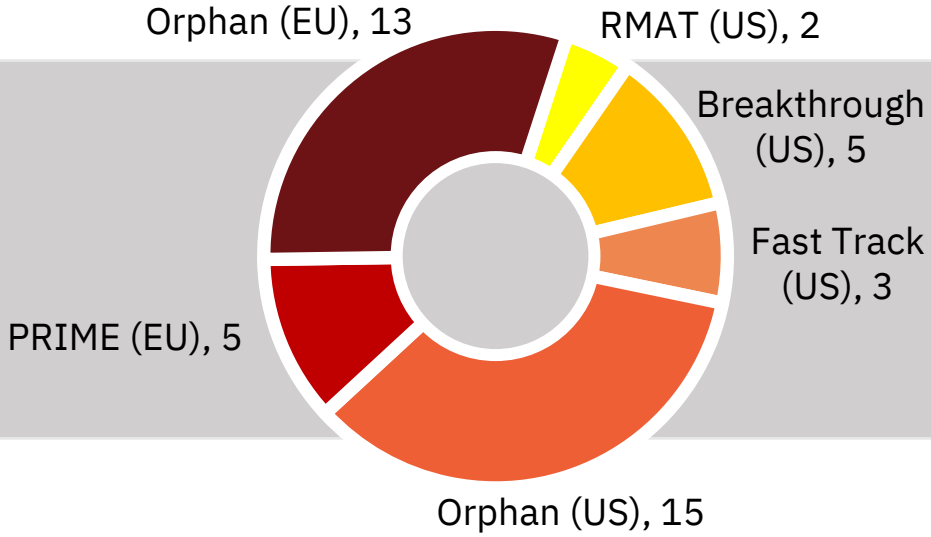


Total Global Financings
Inherited Blood Disorders

$2.3B

↑ **26%** from 2017

Regulatory Designations in Inherited Blood Disorders



*Globally, regulatory agencies have awarded **43 designations** intended to provide expedited pathways to or otherwise incentivize the development of innovative therapies for inherited blood disorders.*

All data and figures calculated through the end of March 2019.

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Sector Commentary

Alison Finger
Chief Commercial Officer
bluebird bio

Inherited blood disorders are good candidates for gene therapy for many different reasons. One of the biggest is the opportunity to address the underlying genetic cause of an inherited blood disorder by modifying a patient's hematopoietic stem cells (HSCs).

There have been incredible advances in the science within the gene therapy landscape in recent years. A key breakthrough has been the extensive improvements made to viral vectors, which act as the delivery vehicle for the selected gene of interest. With respect to bluebird bio's gene therapy platform, more recent breakthroughs include refinements to how we collect patients' hematopoietic stem cells, and improvements made to the drug product manufacturing process.

While significant scientific innovation has advanced, a key remaining challenge is the commercialization and reimbursement of these treatments. At bluebird bio, we are taking that same innovative spirit that drives our science to work together with stakeholders toward establishing treatment centers that can fully support the patient journey, as well as pioneering new pricing and reimbursement models that responsibly reflect the value that a one-time transformational treatment brings to patients, families, the healthcare system, and society.

Our investigational gene therapies are being developed as one-time treatments that potentially address the underlying genetic cause of the disease. One of our potential gene therapy potential treatments is for transfusion-dependent beta thalassemia (TDT), a severe genetic disease caused by mutations in the β-globin gene, which result in reduced or absent hemoglobin. In order to survive, people with TDT maintain hemoglobin levels through lifelong chronic blood transfusions. These transfusions carry the risk of progressive multi-organ damage due to unavoidable iron overload. The goal of treatment with our investigational gene therapies is to enable patients with TDT to produce hemoglobin at sufficient levels, reduce iron overload, and to allow independence from blood transfusions. This therapy, and others like it, have the potential to positively impact the lives of thousands of patients across the world.

We want to ensure lives are lived fully and make sure gene therapy can be accessible to all who can benefit. This is a personal mission for all of us bluebird and we care deeply about the people we can help with our therapies. Our ambition is to recode science, systems and the status quo – for life.

Dan Levin
Global Commercial Development & Hemophilia Marketing Lead
Pfizer

At ARM's 2018 Meeting on the Mesa, speaking on a panel on gene therapies for hemophilia:

"I've spent my career in hemophilia, so I look at [gene therapy] from two different aspects. One is that hemophilia is a great target because of the technical and clinical aspects of the disease – it's well-characterized, a single gene, there's really good surrogate endpoints that are good representatives of clinical endpoints – but what's most important to me, knowing these patients and these caregivers, is really the unmet need. [...]

"There are treatments, and they're good treatments, that have been developed and honed over many, many years. But make no mistake – daily, weekly, regular infusions are very, very invasive for these patients. And while they've done an excellent job coping with that – and certainly the subcutaneous therapies that are coming out now certainly make that better, and extended half-lives make that better – they're still invasive, and even the newer therapies are still disruptive. So at the end of the day, hemophilia is a great target from a clinical and technical standpoint and it also has a lot of unmet need."

"One of the experiences I've had over a long time is working with the World Federation of Hemophilia, and they say 75 percent of people worldwide with bleeding disorders are still undertreated or untreated. So when we think about where do we go first [...] the developing world is very compelling also, certainly from a need-based perspective. So this idea of leapfrogging and bringing some of these countries directly to gene therapy is incredibly enticing, incredibly exciting. That is one of the things we're looking at and thinking about, you know, are there ways to do that in a in a transformative way."

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