Genetic Innovation for All

AnGes Company Guide

Business Overview

AnGes is a biopharmaceutical company and a global leader in gene-based medicines, dedicated to developing innovative therapies.

The gene-based medicines we develop are a new class of biopharmaceuticals that harness the functions of genes. Such medicines are generally referred to as nucleic-acid therapeutics or gene therapy products. We actively collaborate with academic institutions and biotech ventures in Japan and around the world to drive the development of new gene-based medicines.

New medicines and therapeutic approaches continue to emerge globally, with genome-editing treatments at the cutting edge. Our subsidiary, EmendoBio, is developing high-precision genome-editing technologies using proprietary nucleases.

Furthermore, to meet the needs of patients waiting for treatments affected by a situation in which drugs approved elsewhere have not been approved in Japan, a phenomenon known as drug lag or drug loss, we are working to introduce therapeutics that treat rare diseases and are already available overseas into the Japanese market.

In addition to developing and introducing these pharmaceuticals, we also operate a diagnostics business aimed at enabling the early detection and early treatment of rare genetic diseases.

Corporate Philosophy

Mission

Unlocking the power of genes to create a future where treatment is available to all.

Vision

As a global leader in gene-based medicines, we will deliver innovation for diseases for which effective treatments are still unavailable, helping improve people's quality of life (QOL) worldwide.

Values

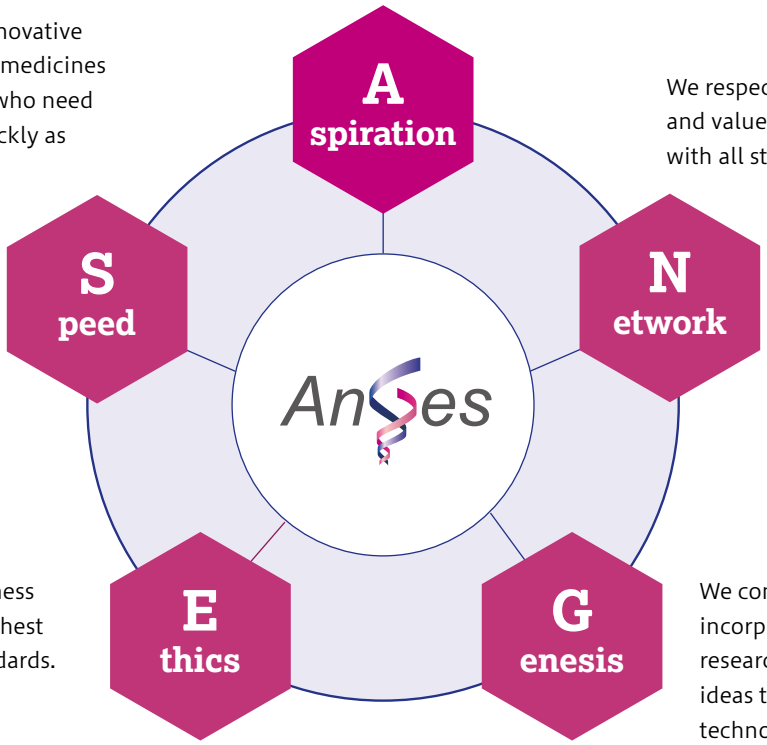
A spiration
We maintain a spirit of challenge and enthusiasm, embracing change to become agents of transformation.

S peed
We bring innovative gene-based medicines to patients who need them as quickly as possible.

N etwork
We respect diversity and value our network with all stakeholders.

E thics
We do business with the highest ethical standards.

G enesis
We constantly incorporate the latest research findings and ideas to create new technologies, products, and value.



Our Name's Origin

AnGes derives from ange, the French word for "angel." It also evokes terms related to our field of pharmaceutical development, such as "angiogenesis" and "anti-gene."

Message from the CEO

"As a Global Leader in Gene-Based Medicines"

Japan, a nation of longevity, has established the only model of its kind in the world, where everyone has access to medical care through its universal health insurance system. While Japan's pharmaceutical market once accounted for 20% of the global market, it has now declined to 6%. One of the reasons for this decline is a decrease in drug discovery capabilities. In the United States, 80% of the top 10 best-selling drugs originate from the inventions and discoveries of biotech startups, which have contributed significantly to global drug discovery. In Japan, there is a strong need to improve our drug discovery capabilities.

In 1984, HGF (hepatocyte growth factor), a factor that promotes the growth of liver cells, was discovered in Japan. When I was engaged in research and development in my previous role, focusing on cloning the HGF gene for hepatocyte regeneration, I distinctly recall feeling that this discovery would bring hope to people worldwide.
And joining AnGes, which was founded to commercialize HGF as a pharmaceutical product,may have been both a fortunate and natural step for me.
AnGes' mission, as our corporate philosophy, is to "unlock the power of genes to create a future where treatment is available to all." Our vision, the goal we strive for, is "as a global leader in gene-based medicines, we will deliver innovation for rare diseases and intractable diseases that still lack effective treatments and help improve quality of life (QOL) for people worldwide." We hope that by advancing toward the realization of our corporate philosophy, we can contribute to the improvement of Japan's drug discovery capabilities.

In addition to developing gene-based medicines, such as HGF gene therapy products using plasmid DNA and nucleic acid medicines like NF-κB decoy oligonucleotide that utilize the functions of genes, we are also engaged in contract testing for rare genetic diseases and the research and development of therapeutic methods using cutting-edge genome-editing technologies. By leveraging the world's most advanced ideas and modalities, we are challenging ourselves to create new drugs and treat rare diseases in order to realize our corporate philosophy. To this end, we will promote international research and development, not only in Japan but also on a global scale. Furthermore, by accelerating the discovery and development of innovative medicines, we will spearhead building the foundations for a high-value-added pharmaceutical industry and a Japan-centered global ecosystem that circulates worldwide.
Our true goal is to deliver one-of-a-kind treatments to patients who have no other effective therapeutic options and are eagerly awaiting new drugs. Toward this goal, we will conduct our business on a global stage, working with our experienced staff and with the cooperation of various external parties to achieve great results with a small, elite team.
We will continue to strive to meet the expectations of the many people who are waiting for new treatments.

President & CEO **Ei Yamada**

Business Fields

Products in Development

We are developing novel modalities, such as gene-based medicines, for diseases that previously had no treatment or were difficult to treat.

■ AnGes Pipeline

Area	Partner	Indication	Basic Research / Preclinical Study / Phase 1 / Clinical Study Phase 2 / Phase 3 / Application for Approval / Approval
HGF Gene Therapy Product			
Japan	—	Arteriosclerosis obliterans	Completed
U S A	—	Chronic Limb-Threatening Ischemia	Completed → Positive results → Preparing Be granted Breakthrough Therapy designation
NF- κ B Decoy Oligonucleotide			
Japan	—	Chronic discogenic lumbar back pain	On Going
DNA Vaccine			
Aurtralia	—	Hypertension	Completed
Tie2 Agonists			
U S A	Vasomune (共同開発先)	Acute Respiratory Distress Syndrome	On Going

■ EmendoBio Pipeline

Program	Lead Optimization / Preclinical Study / Phase 1 -Phase 3
HEMATOLOGY	
EMD-101 Severe Congenital Neutropenia	
CARDIOVASCULAR	
EMD-301 Familial Hypercholesterolemia	
EMD-302 Hyperlipidemia	
OPHTHALMOLOGY	
EMD-201 Retinitis Pigmentosa	
EMD-202 Cone-Rod Dystrophy	
EMD-203 Macular Dystrophy	

HGF Gene Therapy Product (Beperminogene Perplasmid)

1-year post-amputation mortality in CLTI

Approximately 20%

The global number of CLTI patients

2 million people

■ Target Disease

Mild to moderate chronic limb threatening ischemia (CLTI) with lower limb ulcers

CLTI is a condition in which the arteries in the lower limbs become stenosed or occluded, causing a severe ischemic state where oxygen and nutrients are deficient.

■ Current Treatments and Issues

Current treatments include catheter treatment and bypass surgery, but if the ischemic state persists, it can lead to lower limb ulcers and gangrene. If the symptoms progress, it may result in amputation of the lower limb and can ultimately become life-threatening.
Without revascularization, a lower limb is amputated every 20 seconds worldwide due to CLTI. Furthermore, the one-year mortality rate is reported to be about 20%, which is comparable to the one-year mortality rate for stage III gastric cancer.

■ Mechanism of Action

Utilizing the angiogenic function of HGF (hepatocyte growth factor)

HGF, a protein that promotes the proliferation of liver cells, is involved in liver regeneration and tissue repair. In addition to liver regeneration, HGF is also known to be involved in angiogenesis (the formation of new blood vessels). The HGF gene therapy product incorporates the gene that produces HGF into a plasmid DNA. By injecting this product into the site of arterial stenosis or occlusion, new blood vessels are formed at the injection site, improving blood flow and alleviating symptoms.

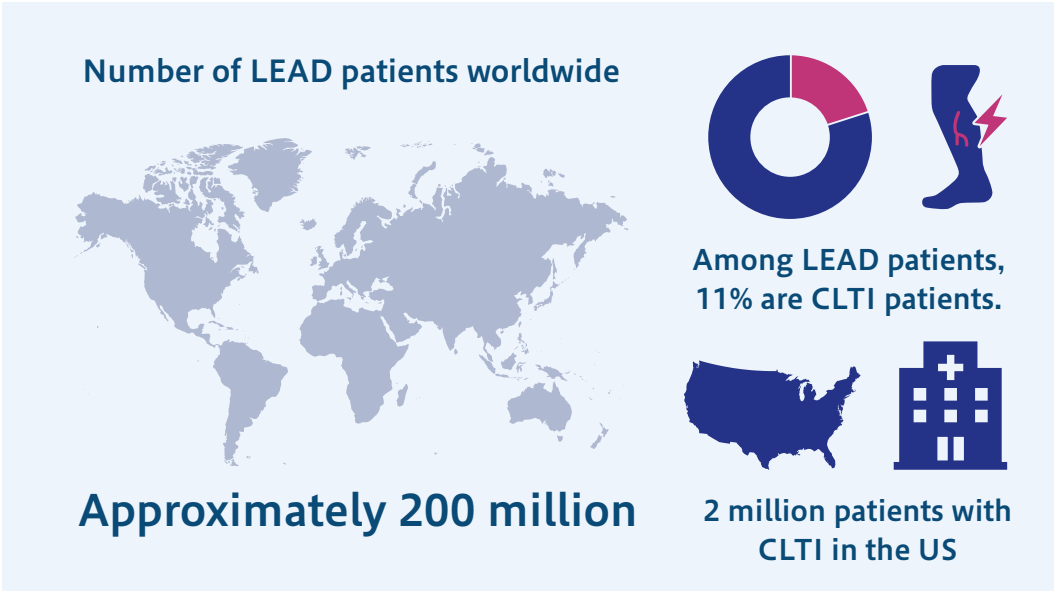
■ Number of CLTI Patients

The number of patients with lower extremity arterial disease (LEAD) is increasing worldwide, with an estimated 200 million people affected. Among these LEAD patients, it is estimated that about 11% have chronic limb threatening ischemia (CLTI), which is

complicated by pain at rest, ischemic ulcers, and other symptoms.
There are an estimated 2 million patients in the United States.

■ AnGes' Initiatives

In 1995, Professor Ryuichi Morishita of Osaka University discovered that HGF has the ability to create new blood vessels. Since our founding in 1999, we have been working on the development of a therapeutic agent utilizing HGF.
In Japan, because gene therapy is a new modality, we have pursued development targeting severe critical limb ischemia. In 2019, our HGF gene therapy product became the first plasmid DNA-based treatment to receive conditional and time-limited approval in the world.
Meanwhile, in the United States, based on the advice of lead clinical trial investigators and others, we began a Phase II clinical trial in 2020 targeting mild to moderate CLTI, aiming to prevent progression to severe disease at an earlier stage. In June 2024, it was confirmed that the results of the clinical trial in the United States were extremely positive. Following these results, in June of the same year, we decided to reconsider our product development and sales policy in Japan. In the United States, due to the positive clinical trial results, the product received Breakthrough Therapy designation from the FDA in September of the same year.
Given these circumstances, we are prioritizing commercialization in the United States and focusing our development efforts there to obtain marketing approval as quickly as possible.
In consultation with the FDA, we have concluded our clinical trials and are proceeding with preparations for a Biologics License Application (BLA). We have also conducted a Type B Clinical Meeting with the FDA and successfully reached alignment on the clinical regulatory strategy for the BLA submission.
In addition, to ensure a stable supply after approval, we have entered into an agreement with Boehringer Ingelheim Biopharmaceuticals for the supply of the drug substance.
We aim to commercialize our HGF gene therapy product as a treatment that improves blood circulation without the need for endovascular therapy or bypass surgery, thereby helping patients avoid limb amputation and life-threatening risks.



NF- κ B Decoy Oligonucleotide DNA

■ Target Disease

Chronic discogenic low back pain

Discogenic low back pain is a chronic (lasting more than three months) low back pain caused by damage or degeneration of the intervertebral discs. It frequently occurs in people up to 45 years of age, and is thought to account for 40% of all chronic low back pain.

Since normal intervertebral discs have very few nerves, damage to the disc itself does not cause much pain. However, when the outer annulus fibrosus of the disc is damaged, blood vessels accompanied by nerves penetrate the inner part of the annulus for repair. As a result, nerves distribute to the inner part of the disc, which should not normally feel pain, causing pain to occur when a load is applied to the disc.

Furthermore, it has been reported that various inflammatory substances are produced when the annulus fibrosus is damaged due to excessive load on the intervertebral disc. In animal models of intervertebral disc injury, it has been reported that various cytokines and neurotrophic factors are released from the nucleus pulposus and annulus fibrosus cells. The expression of these cytokines and neurotrophic factors has also been reported in human pathological intervertebral discs collected during surgery.

■ Current Treatments and Issues

Currently, there is no fundamental cure. It is treated with symptomatic therapies such as drug therapy, exercise therapy, and intradiscal electrothermal therapy (IDET).

◎ Drug Therapy

When there is pain and swelling due to low back pain or inflammation, antipyretic analgesics called non-steroidal anti-inflammatory drugs (NSAIDs) are used.

◎ Exercise Therapy

After the pain has subsided with drug treatment, rehabilitation and exercise therapy by a doctor or physical therapist can speed up recovery.

◎ IDET Treatment

Using X-rays, a needle is inserted into the intervertebral disc, and heat is applied to the tip of the needle to numb the nerves in the disc, making them less likely to feel pain. In addition, the collagen fibers of the intervertebral disc harden and stabilize the disc, which helps prevent pain from occurring.

■ Mechanism of Action

NF- κ B is a protein complex that acts as a transcription factor and is normally inactivated by binding to the I κ B α protein located in the cytoplasm. When a cell is

stimulated, the I κ B kinase (IKK) complex is activated and phosphorylates the inhibitory protein (I κ B α). As a result, I κ B α is degraded, NF- κ B is released, the nuclear localization signal transduction site that was inhibited by I κ B α is exposed, and NF- κ B translocates to the nucleus and is activated. Once in the nucleus, NF- κ B binds to its target genes (GGGACTTTCC or similar DNA sequences) and induces their expression. The cells then proliferate and differentiate, causing biological responses such as inflammation and immune reactions.
In chronic discogenic low back pain, it is considered that damage and degeneration of the intervertebral disc cause the release of cytokines, which in turn activate NF- κ B, leading to excessive immune and inflammatory responses. By administering NF- κ B decoy oligonucleotide DNA (a decoy oligonucleotide nucleic acid), which prevents NF- κ B from binding to DNA, the action of NF- κ B is suppressed.
While the effects of conventional symptomatic treatments like drug therapy were often short-lived, with the administration of NF- κ B decoy oligonucleotide DNA, over 75% of patients confirmed pain improvement up to one year later, and an improvement in intervertebral disc height was also observed. (From the U.S. Phase Ib clinical trial)

■ Number of Chronic Discogenic Low Back Pain Patients

In a national survey conducted by the Japanese Society for the Study of Low Back Pain in 2023, the prevalence of chronic low back pain (lasting three months or more) was reported to be approximately 11.5%. Among patients with chronic low back pain, the percentage in which the intervertebral disc is the main cause of pain varies by study, but has been reported to be approximately 55%. The number of patients with chronic discogenic low back pain is estimated to correspond to about 6.3% of the total population, by multiplying the prevalence of chronic low back pain (11.5%) by the prevalence of discogenic low back pain (55%). Considering Japan's total population (approximately 125 million), it is possible that about 7.87 million people suffer from chronic discogenic low back pain.

■ AnGes' Initiatives

We have been engaged in the research and development of NF- κ B decoy oligonucleotide DNA since 2002, exploring its potential as a therapeutic agent for various diseases and symptoms presumed to be caused by the activation of NF- κ B. In 2018, we initiated a Phase I clinical trial in the United States for the treatment of discogenic low back pain. In 2021, the results of the clinical trial confirmed the safety of the drug, with high patient tolerability and no serious adverse events observed.
Furthermore, a single administration of NF- κ B decoy oligonucleotide DNA resulted in early pain improvement. One year later, the pain score in the placebo group had decreased by an average of 40.3% (median 32.8%) compared to pre-administration, whereas the 10 mg treatment group showed an average reduction of 77.4% (median 97.5%). On closer inspection, pain almost completely disappeared in half of the patients.
Additionally, the increase in the height of the intervertebral disc between the lumbar vertebrae compared to pre-administration suggests an improvement in the damaged disc. Such effective results have not been reported with other therapeutic drugs.
Subsequently, we began a Phase II clinical trial in Japan in 2023 and signed an agreement with Shionogi & Co., Ltd. to collaborate on domestic clinical trials.

DNA Vaccine

■ Target Disease

Hypertension

Blood pressure is the pressure exerted on the inside of the artery walls as blood flows through them. The upper number, systolic blood pressure (the maximum pressure), is the pressure when the heart contracts to pump blood out. While the lower number, diastolic blood pressure (the minimum pressure), is the pressure when the heart is relaxed. A diagnosis of hypertension is made when systolic blood pressure (the upper number) is 140 mmHg or higher, or diastolic blood pressure (the lower number) is 90 mmHg or higher.

There are various causes for increased blood pressure, one of which is the constriction of blood vessels. Angiotensin II is one of the substances that causes this constriction. Angiotensin II is a type of hormone produced in the body. It also promotes the secretion of aldosterone, a hormone that acts on the kidneys to increase circulating plasma volume, thereby raising blood pressure.

■ Current Treatments and Issues

Currently, treatments for hypertension include drugs such as calcium channel blockers, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, diuretics, and beta-blockers, which generally need to be taken daily.

With treatments that improve hypertension by dilating blood vessels or suppressing the action of substances that raise blood pressure, it is not uncommon for patients to continue taking the medication for life once they start. If blood pressure remains stable within the normal range for a long period, it may be possible to stop taking the medication, but stopping may cause the blood pressure to rise again.

■ Mechanism of Action

A gene that produces a protein with a sequence identical to part of angiotensin II is incorporated into a plasmid and administered as a DNA vaccine. Normally, the body does not produce antibodies against angiotensin II. However, the DNA vaccine creates a pseudo-virus with a shortened angiotensin II sequence, which the immune system recognizes as an antigen, leading to the production of antibodies. Subsequently, when angiotensin II is produced in the body, these antibodies inhibit its function, preventing a rise in blood pressure.

■ AnGes' Initiatives

Utilizing the expertise in plasmid-based gene medicines cultivated through our HGF gene therapy product, we began research and development of a DNA vaccine for treating hypertension in 2016. In 2017, we submitted a clinical trial notification in Australia, and in 2018, we began patient enrollment. In 2021, the clinical trial results showed no serious adverse events, confirming the vaccine's safety and the production of antibodies against angiotensin II.

With our DNA vaccine, we aim to develop a new treatment that eliminates the need for the daily medication required by conventional therapies.

Tie2 Receptor Agonist (AV-001) (Co-Developed Product)

■ Target Disease

Acute respiratory distress syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is a general term for a condition characterized by acute-onset hypoxemia with a preceding underlying disease or trauma. Chest X-rays show bilateral pulmonary infiltrates, and the cause cannot be fully explained by heart failure, renal failure, or intravascular fluid overload alone. It is characterized by severe hypoxemia that does not improve with standard oxygen administration alone. It is a severe acute respiratory failure that occurs secondary to various underlying conditions such as sepsis, pneumonia, aspiration, drowning, burns, trauma, and acute pancreatitis, developing within one week of a direct or indirect insult to the lungs. In ARDS, severe inflammation of the lungs occurs with injury to the vascular endothelium and alveolar epithelium, leading to increased permeability of the pulmonary microvascular endothelium and alveolar epithelium. As a result, fluid leaks and accumulates in the interstitium around the blood vessels and bronchi, leading to a state of interstitial pulmonary edema. Furthermore, if the alveolar epithelium is also injured, the alveolar spaces fill with exudate containing plasma components, resulting in a state of alveolar pulmonary edema.

■ Current Treatments and Issues

Unfortunately, no drug is currently known to directly improve the survival rate of patients. Steroids, which have anti-inflammatory and immunosuppressive effects, are used to suppress the lung inflammation that causes ARDS. In moderate to severe cases, muscle relaxants may be used to support mechanical ventilation.

◎ Drug Therapy

Drugs are used to assist with labored breathing. Low-dose steroids are recommended for ARDS drug therapy. Steroids have anti-inflammatory and immunosuppressive effects. If the condition is judged to be moderate to severe, the use of muscle relaxants is also considered to stabilize and manage breathing by reducing the patient's spontaneous respiratory efforts and allowing the ventilator to take over.

◎ Respiratory Therapy

In ARDS, lung damage causes symptoms such as difficulty breathing. Because of this, the first priority is to enable a patient to breathe smoothly. Oxygen administration and respiratory support are provided using high-flow nasal cannula oxygen therapy with nose tubing or an oxygen mask.

When using a mechanical ventilator, there is a risk of ventilator-associated lung injury, where over-inflation or excessive pressure can damage the lungs. This risk can be minimized by properly adjusting the pressure, such as the positive end-expiratory pressure (PEEP), and operating the ventilator correctly.

Tie2 Receptor Agonist（AV-001）（Co-Developed Product）

■ Mechanism of Action

AV-001 activates the Tie2-angiopoietin signaling axis, stimulating multiple downstream pathways to enhance endothelial cell stability, restore normal barrier defense, and normalize the vasculature. This vascular normalization may consequently prevent vascular leakage and improve the vascular dysfunction that affects the underlying pathophysiology in patients with conditions such as bacterial and viral ARDS, sepsis, hemorrhagic shock, acute kidney injury, stroke, and vascular dementia. Importantly, in multiple preclinical studies using experimental animals, AV-001 strengthened the junctions between endothelial cells and promoted their survival, which led to reduced pulmonary edema, improved lung function, and significantly improved survival rates.

■ Number of ARDS Patients

An epidemiological study in Washington State, USA, published in 2000, reported that 64 per 100,000 people develop ARDS annually. The mortality rate after ARDS onset is approximately 40%, indicating a very poor prognosis.

According to data from multiple U.S. studies, approximately 10-15% of patients admitted to intensive care units（ICUs）are reported to develop ARDS. The U.S. National Heart, Lung, and Blood Institute（NHLBI）task force on respiratory distress syndromes estimates the incidence of ARDS in the United States to be 150,000 cases per year.

■ AnGes' Initiatives

Since 2018, we have been co-developing AV-001, a therapeutic agent for ARDS, with Vasomune Therapeutics, a Canadian biopharmaceutical company（Vasomune）. Vasomune was founded in Toronto, Canada, in 2014, and focuses on vascular normalization strategies. It is developing AV-001, which was discovered and designed at the Sunnybrook Research Institute at Sunnybrook Hospital.

Through the development of AV-001, we aim to commercialize a therapeutic agent that improves lung function in patients with ARDS.

In addition, in 2025, we will initiate a new physician-sponsored clinical study to evaluate whether our approach can reduce cytotoxic cerebral edema—which impairs cognitive function as a result of hemodialysis—and preserve white matter function in the brain. The first patient was enrolled in January 2026.

To explore the potential application of our technology to disease areas involving vascular leakage, including such new indications, we have entered into a new co-development agreement for AV-001 with Vasomune.

Genome-Editing Therapies (Developed by Our Subsidiary, EmendoBio)

Our subsidiary, EmendoBio Inc., aiming to safely apply genome-editing in medical application, has established a platform technology (OMNI Platform) for discovering and optimizing novel CRISPR nucleases. They have created and filed patents for many new nucleases (OMNI Nucleases) with novel features, including the ability to avoid the "off-target effects" that are often a concern with genome-editing.

■ Features of EmendoBio's Genome-Editing Technology

What Is Genome-Editing?

Genome-editing is a technology that modifies genes using DNA cleavage enzymes (nucleases) that cleave only specific base sequences (target sequences).

Avoiding Off-Target Effects

With previous technologies, there was a concern about "off-target effects," where genes other than the intended target are cleaved. EmendoBio's technology improves the nuclease to reduce these off-target effects, aiming to establish a safer genome-editing technology for medical applications.

- Developed a method to rapidly create nucleases for each target sequence that do not cleave unless it is 100% complementary
- Although the versatility of the DNA cleavage enzyme is compromised, its high specificity contributes to improved safety
- Even if similar sequences exist elsewhere in the genome, they are not cleaved, allowing greater freedom to select target sequences

Establishment of a Proprietary Platform (OMNI Platform)

EmendoBio creates numerous OMNI Nucleases with new features, selects the most suitable nuclease, and further optimizes it for the target sequence.
Through the discovery and optimization of new nucleases, they are advancing the development of safe and effective treatments.

■ Target Disease

ELANE-related severe congenital neutropenia

ELANE is the name for the neutrophil elastase gene. Neutrophils normally differentiate and mature continuously from hematopoietic stem cells in the body. However, when there is an abnormality in the ELANE gene, abnormal proteins are produced when this gene becomes active in cells at the time of differentiation into neutrophils. This prevents the neutrophils from maturing, resulting in a decrease in the neutrophil count.
Due to the marked neutropenia from early infancy, patients experience recurrent otitis media, respiratory tract infections, cellulitis, and skin infections caused by staphylococci and streptococci. Severe infections such as pneumonia and sepsis also occur. By about the age of two, they also develop oral ulcers and painful gingivitis and stomatitis. Diffuse gastrointestinal lesions can also cause abdominal pain and diarrhea similar to Crohn's disease.

■ Current Treatments and Issues

Infection prevention is crucial, requiring daily administration of trimethoprim/sulfamethoxazole, antifungal drugs if necessary, and oral care by a dentist. Side effects of trimethoprim/sulfamethoxazole, such as rashes and blood disorders, require caution. In addition, hematopoietic cell transplantation is increasingly chosen as a curative treatment, but the optimal timing for this procedure has not been established.

■ Mechanism of Action

Treating this disease requires removing the abnormal gene.
We inherit one set of genes from our father and from our mother. While their DNA sequences are usually almost identical, a difference in just one place on one of the genes can cause a genetic disease. In diseases caused by a gene abnormality that results in a protein with a harmful function, it is necessary to delete the abnormal gene to prevent the production of that harmful protein. Fortunately, since we have genes from both parents, deleting the one abnormal gene allows the other normal gene to function, which is expected to enable the normal differentiation and maturation of neutrophils. However, it is crucial not to damage the normal gene in the process. This requires the precision to distinguish the difference in one place between the two genes inherited from the parents and edit only the abnormal gene without damaging the normal one. The risk of accidentally editing an unrelated gene with a similar DNA sequence (off-target effect) must be minimized as much as possible.

■ Number of ELANE-Related Severe Congenital Neutropenia Patients

The prevalence is 1 in 250,000, although it is likely underdiagnosed.
Approximately 16,000 patients worldwide.

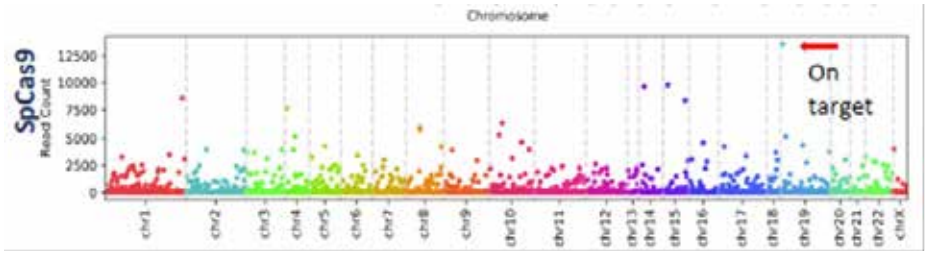
Genome-Editing Therapies（Developed by Our Subsidiary, EmendoBio）

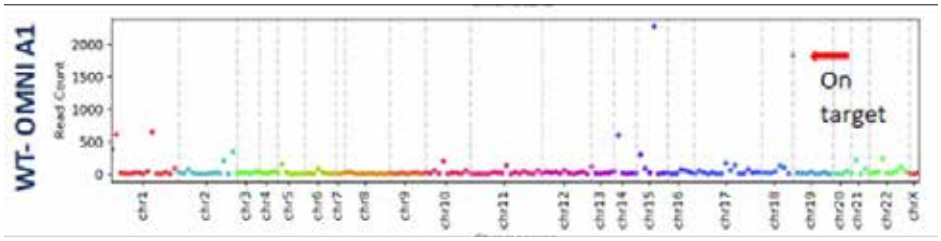
■ AnGes' Initiatives

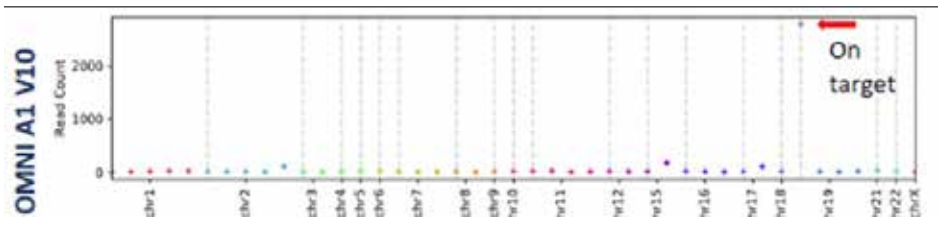
We invested in EmendoBio in 2019 and subsequently made it a subsidiary in 2020, fully embarking on the development of genome-editing technology.
EmendoBio has developed numerous proprietary DNA cleavage enzymes（nucleases）and is advancing the development of nucleases（OMNI Nucleases）which enable highly accurate genome-editing with few off-target effects, which cleave sites other than the target site. By optimizing the OMNI Nucleases, the occurrence of off-target effects can be suppressed, enabling highly accurate genome-editing.
EmendoBio's high-precision genome-editing technologies represent a foundational platform required for the safe execution of genome-editing therapies, and we are continuing to advance their development to support the future growth and advancement of the genome-editing field.

Other Products in Development at EmendoBio

Dyslipidemia, including homozygous familial hypercholesterolemia
Atherosclerotic cardiovascular disease（ASCVD）
A1AD
Macrophages
Various immuno-oncology applications







In-Licensing Business

We are working to introduce pharmaceuticals into the Japanese market that are available overseas but not in Japan. In particular, many treatments for rare diseases with small patient populations are not yet available in Japan. We collaborate with physicians treating these patients in Japan to obtain marketing approval in a short period of time.

Zokinvy (Product)

■ Target Disease

Hutchinson-Gilford progeria syndrome (HGPS) and processing-deficient progeroid laminopathies (PDPL)

These are diseases known as progeria, or "premature senescence" syndromes, in which mortality increases at an accelerated rate from a young age. HGPS is caused by a point mutation in the LMNA gene, which leads to the production of progerin, a mutated and farnesylated (*1) protein.

In PDPL, mutations in the LMNA or ZMPSTE24 genes lead to the production of farnesylated proteins similar to progerin, which accelerates senescence.

Both disease types present with premature senescence symptoms, including severe growth failure, scleroderma-like skin, systemic lipodystrophy, alopecia, joint contractures, skeletal dysplasia, and accelerated atherosclerosis. Death occurs at a young age due to atherosclerotic disease (myocardial infarction or stroke), with the average age of death in HGPS reported as 14.5 years.

*1 Farnesylation: A type of protein modification. A farnesyl group is attached to the end of a protein by farnesyltransferase. The protein, now with a hydrophobic end, inserts this part into the cell membrane, anchoring the protein to the cell membrane, or the inner membrane of nuclear membrane. This causes the farnesylated protein to exist on the cell or nuclear membrane without being properly metabolized.

■ Mechanism of Action

Zokinvy inhibits the accumulation of the farnesylated mutant proteins caused by the aforementioned gene mutations.

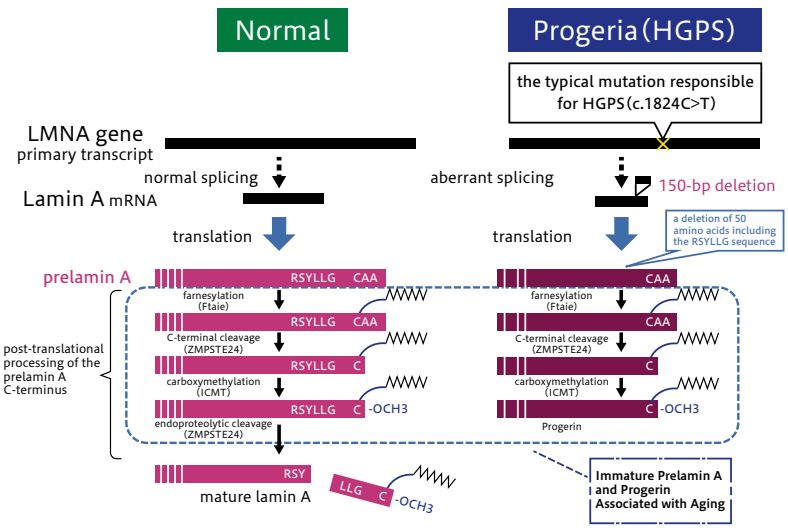
■ Number of Patients

HGPS occurs in approximately 1 in 4 million births, with about 140 patients worldwide. There are about 50 patients with PDPL worldwide.

■ AnGes' Initiatives

Zokinvy was approved and launched in the United States in November 2020, and was subsequently approved in the European Union and the United Kingdom. We acquired the exclusive marketing rights for Japan in May 2022. In March 2023, it received orphan drug designation from the Ministry of Health, Labour and Welfare. It obtained marketing approval on January 18, 2024, was listed on the National Health Insurance (NHI) drug price list on April 17, 2024, and was launched on May 27, 2024.

We have entered into a joint research agreement with OptimAIze Consulting, an AI startup originating from the Faculty of Medicine at the University of Tokyo. Leveraging proprietary AI-driven analyses, we will examine efficient strategies to significantly reduce research and development timelines and costs, and explore the potential for developing new therapeutic indications.



Diagnostics Business

In April 2021, we established the AnGes Clinical Research Laboratory (ACRL), a hygiene inspection laboratory primarily focused on testing for rare genetic diseases.
Many rare genetic diseases have few characteristic symptoms, making them difficult to detect through standard diagnostic methods. When treating these rare genetic diseases, it is crucial to start as early as possible after the symptoms appear, preferably before the onset of symptoms. While an increasing number of rare genetic diseases are becoming treatable, for some, the desired therapeutic effect cannot be achieved unless treatment begins before symptoms appear.
After its establishment, ACRL were contracted to perform expanded newborn screening tests. Initially, we were contracted by the Clinical & Research Association for Rare, Intractable Diseases (CReARID) to perform their "Optional Screening" service in the expanded newborn screening tests. However, since August 2024, we have been directly contracted by municipalities and their affiliated organizations to conduct expanded newborn screening tests.
Furthermore, in conjunction with the launch of Zokinvy in May 2024, we established a system for genetic testing as a definitive test for its target diseases, Hutchinson-Gilford progeria syndrome (HGPS) and processing-deficient progeroid laminopathies (PDPL), and have begun accepting contracts for these services.
In addition to screening tests, we have also begun offering contract services for confirmatory and genetic testing and biomarker testing, enabling us to provide comprehensive diagnostic services covering the entire spectrum from screening and diagnosis to treatment for rare inherited diseases.
In particular, by utilizing biomarker testing as a secondary screening tool to address false positives that may arise in mucopolysaccharidosis screening, we are helping to reduce the burden on examinees, their families, and healthcare professionals.

Screening for 14 diseases, the largest number in Japan

For rare genetic diseases, a sufficient therapeutic effect cannot be obtained unless they are detected early, before symptoms appear, and treatment is started at the appropriate time.
Since these diseases are rare, many are difficult to identify in routine clinical practice, and by the time they are found, the symptoms may have already progressed.

	Disease	Screening Method	Treatment
1	Mucopolysaccharidosis (MPS) Type I	Dried blood spot enzyme activity	Enzyme replacement therapy, hematopoietic stem cell transplantation
2	Mucopolysaccharidosis (MPS) Type II	Dried blood spot enzyme activity	Enzyme replacement therapy, hematopoietic stem cell transplantation
3	Mucopolysaccharidosis (MPS) Type IVA	Dried blood spot enzyme activity	Enzyme replacement therapy
4	Mucopolysaccharidosis (MPS) Type VI	Dried blood spot enzyme activity	Enzyme replacement therapy, hematopoietic stem cell transplantation
5	Mucopolysaccharidosis (MPS) Type VII	Dried blood spot enzyme activity	Enzyme replacement therapy, hematopoietic stem cell transplantation
6	Fabry Disease	Dried blood spot enzyme activity	Enzyme replacement therapy, chemical chaperone
7	Pompe Disease	Dried blood spot enzyme activity	Enzyme replacement therapy (as early as possible after birth for infantile-onset type)
8	Gaucher Disease	Dried blood spot enzyme activity	Enzyme replacement therapy
9	Niemann-Pick Disease Type A/B	Dried blood spot enzyme activity	Enzyme replacement therapy
10	Krabbe Disease	Dried blood spot enzyme activity	Hematopoietic stem cell transplantation (as early as possible after birth for infantile-onset type)
11	Adrenoleukodystrophy (ALD)	C26: 0-lysophosphatidylcholine	Cerebral type: Hematopoietic stem cell transplantation (immediately after onset)
12	Spinal Muscular Atrophy (SMA)	Quantitative PCR for SMN1 gene	Antisense nucleic acid drug, gene therapy (as early as possible after birth for infantile-onset)
13	Severe Combined Immunodeficiency (SCID)	Quantitative PCR for TREC	Hematopoietic stem cell transplantation
14	Adenosine Deaminase Deficiency	ADO	Enzyme replacement therapy, hematopoietic stem cell transplantation

Flexible Contract Types

While some institutions only offer testing items in a fixed package, ACRL can respond flexibly to your needs.

- **Contract for screening testings of all 14 diseases (Municipality #1)**
- **Contract for testing of only some diseases (Municipalities #2 & #3)**

Disease No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Municipality #1	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL
Municipality #2	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	Laboratory A	Laboratory A	–
Municipality #3	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	ACRL	–	–	–	ACRL	Laboratory B	Laboratory B	–

The Only One-Stop Solution in Japan for Rare Genetic Disease Testing

Due to factors such as low profitability, few testing institutions conduct all necessary tests for rare genetic diseases. ACRL, however, is equipped with the systems and functions required for screening tests, genetic tests, and biomarker tests. This allows us to serve as a single point of contact for municipalities and medical institutions, eliminating the need for physicians and municipalities to coordinate with multiple testing institutions.

Corporate Overview

Corporate Citizenship at AnGes (ESG)

As a member of society, AnGes is actively involved in contributing to our community and the environment.

■ **Environment**

● Reducing environmental impact

When printing our AnGes Report for shareholders, AnGes uses environmentally friendly, plant-based eco-inks. These inks do not contain VOCs (volatile organic compounds) and have lower amounts of other harmful components, helping to reduce our environmental impact.

■ **Social**

● Developing innovative medicines for diseases areas with no existing treatments, intractable diseases, and rare diseases

- Developing groundbreaking gene-based medicines (gene therapy, nucleic acid medicines) that harness the power of genes acquired over vast stretches of evolutionary time
- In-licensing and selling medicines in Japan that are not otherwise available, focusing on disease areas with no existing treatments, such as intractable and rare diseases
- Operating a diagnostics business to enable the early detection and early treatment of rare genetic diseases, with a focus on newborns

● Ensuring diversity

In the specialized field of gene-based medicine R&D, securing diverse and talented human resources, including women and minority groups, is essential for the sustainable growth of our company. We are actively expanding opportunities, such as career development and promotion to senior positions for women, aiming to be an organization where many talented female employees can thrive. Our group actively promotes women to management positions and is committed to ensuring diversity.

Trends in the Percentage of Women in Management Positions

■ **Governance**

As a publicly listed company, AnGes' fundamental approach is to fulfill its social mission and responsibilities, ensure the appropriateness of its business operations, maintain and create corporate value, and continuously enhance its corporate governance.

- Management and Operational Execution Structure of AnGes Inc.

We have established a management structure that can respond swiftly and flexibly to changes in the business environment. At the same time, we ensure compliance with laws and maintain management transparency, strengthen the oversight of management and execution, and have a system in place that can earn the trust of our stakeholders.

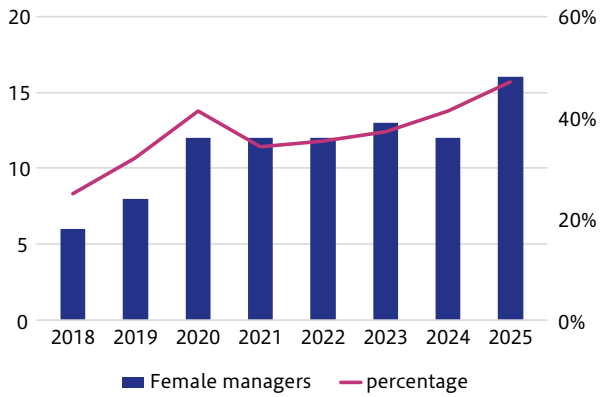
● Board of Directors

- The Board of Directors meets, in principle, once a month to make decisions on important matters related to business execution.
- Three of the five directors are external directors (two of whom are independent directors), responsible for strengthening the management oversight function.

● Board of Auditors

- The Board of Auditors meets, in principle, once a month to discuss and resolve important matters related to auditing. All auditors attend Board of Directors meetings to verify the legality and appropriateness of management decisions made by the directors.
- All three auditors are external auditors, one of whom is a full-time auditor.
- To audit business execution, the full-time auditor and the internal audit staff audit the performance of duties by directors and various departments to ensure their legality and appropriateness. We have a system in place to take necessary measures through an exchange of opinions with the President and CEO.

Women in Management: Trends



Company Information

■ Company Profile

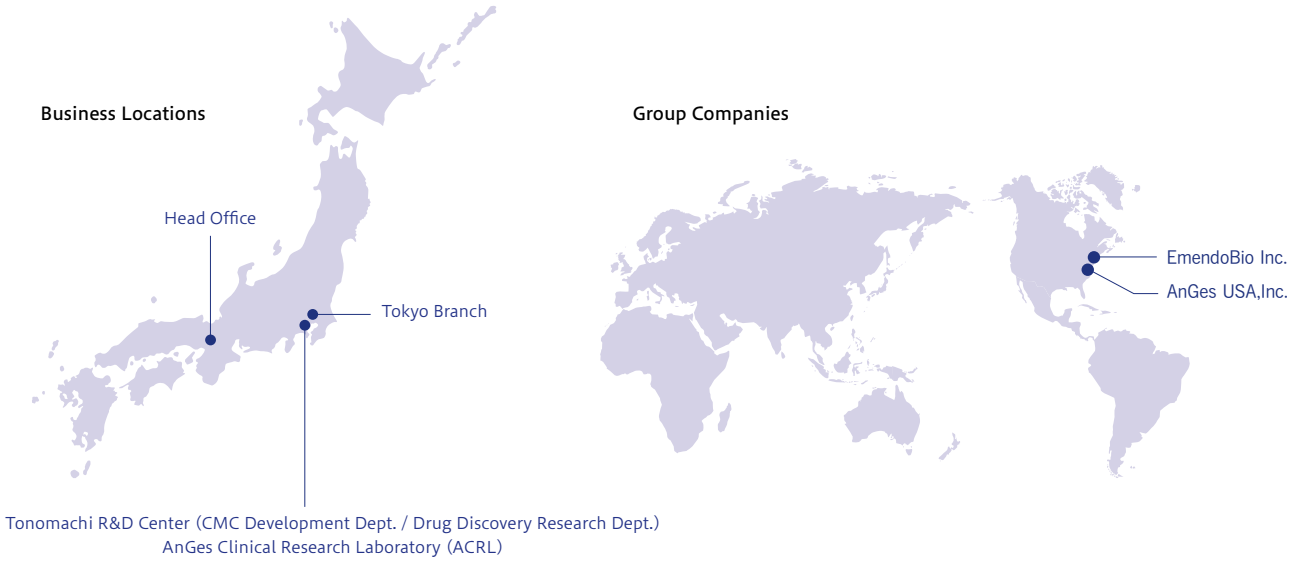
Company Name	AnGes, Inc.
Representative	Ei Yamada（President & CEO）
Date of Establishment	December 17, 1999
Capital Stock	40,228 billion yen（as of December 31, 2025）
Number of Employees	56（consolidated, as of December 31, 2025）
Primary Business	Research and development of gene-based medicines; contract testing for rare genetic diseases

■ Business Locations

Head Office:
Saito Bio-Incubator, 7-7-15 Saito-asagi, Ibaraki, Osaka 567-0085, Japan
Tokyo Branch:
PMO TAMACHI II, 9th Floor, 4-13-3 Shiba, Minato-ku, Tokyo 108-0014, Japan
Tonomachi R&D Center（CMC Development Dept. / Drug Discovery Research Dept.）:
Innovation Center of NanoMedicine, 3-25-14, Tonomachi, Kawasaki-ku, Kawasaki, Kanagawa, 210-0821, Japan
AnGes Clinical Research Laboratory（ACRL）:
Life Science & Environment Research Center, 3-25-13, Tonomachi, Kawasaki-ku, Kawasaki, Kanagawa, 210-0821, Japan

■ Group Companies

AnGes USA, Inc.
111 Town Square Place, Suite 1140, Jersey City, New Jersey, 07310 USA
EmendoBio Inc.
111 Town Square Place, Suite 1140, Jersey City, New Jersey, 07310 USA



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