Healthcare

Strengths in Healthcare area and the development of “AminoScience” and business

The Ajinomoto Group has been developing businesses in the healthcare field, which utilizes the functions of amino acids, since around the time of its founding.
The accumulation of scientific knowledge also bears fruit in the healthcare field.

History of the Ajinomoto Group Healthcare Area

1910s B2B materials business begins with the Company’s founding

1956 Pharmaceutical amino acid business started, supplying essential amino acids for infusion solution

1981 Pharmaceautical enteral nutrition business using amino acids launched

1987 Japan’s first serum-free culture medium introduced

1989 S.A. OmniChem N.V., a contract manufacturer of small molecule drugs in Belgium, acquired (currently S.A. Ajinomoto OmniChem N.V.)

2012 Joint venture Ajinomoto Genexin Co., Ltd. established in South Korea to develop and manufacture biopharmaceutical culture media

2013 Althea Technologies, Inc., a biopharmaceutical contract developer and manufacturer in the United States, acquired (currently Ajinomoto Althea, Inc.)

2016 GeneDesign, Inc., a CDMO for nucleic acid drugs in Japan, acquired

2018 Cambrooke Therapeutics, Inc. acquired, entry into the medical food business supplying products for people with PKU

Ajinomoto Kohjin Bio Co., Ltd. established to manufacture culture media for regenerative medicine

2020 Nualtra Limited, a medical food provider in Ireland, acquired

Taking on the challenge of innovation is one of our strengths in the healthcare field.

The Ajinomoto Group also uses the function of amino acids to develop business in the healthcare field, and launched its first B2B materials business in 1909, the year of the Group's founding. In 1956, we began selling amino acids for medicinal use, and our amino acids were also used in the world's first amino acid infusion solution.

In the 1980s, we developed and launched our own pharmaceutical enteral nutrition and used amino acids as a protein source with excellent digestion and absorption. In addition, we supply amino acids for various pharmaceutical products such as glutamine for gastric ulcer drugs and valine, leucine, isoleucine, and arginine for liver desease treatments. We also introduced animal cell culture medium and Japan's first serum-free culture medium.

We have been especially active in biopharmaceutical and regenerative medicine research in recent years where we are developing applications for "AminoScience." We made a full-scale entry into the production and sales of biopharmaceutical manufacturing media in 2012 with the establishment of a joint venture with Genexine Inc., of South Korea (acquired sole proprietorship in 2023). In 2014, we developed culture media for iPS and ES cells, which are attracting attention in regenerative medicine, and in 2017 we established a joint venture with Kohjin Bio, of Japan, to strengthen our capabilities in regenerative medicine culture media. As with our abilities to develop food and other products, we intend to use our growing knowledge and expertise in scientific research in amino acids to produce products for the healthcare field.

In the bio-pharma service field, we expanded our pharmaceutical contract manufacturing business in 1989 by acquiring the Belgian company S.A. OmniChem N.V., which facilitated joint development and co-creation with customer global pharmaceutical manufacturers.

We strengthened our ability to produce protein drugs and other products for the biopharmaceuticals market by acquiring Althea Technologies, Inc. of the United States, in 2013, and established a contract manufacturing service to cover all volumes from small-lot to mass production of oligonucleotide products by acquiring GeneDesign, Inc. of Japan, in 2016. We have enhanced the structure to provide solutions and services meeting all of our client's needs by effectively utilizing these tangible assets and expanding our unique technologies and services, including AJIPHASE®, an intangible asset of the Ajinomoto Group.

In addition to pharmaceuticals, we will also expand our customer base to the medical food field. We entered the medical food market in 2018 by acquiring U.S. medical food company Cambrooke Therapeutics, Inc. to provide products to patients with the amino acid metabolism disorder phenylketonuria (PKU). Although the number of PKU patients is relatively small, our products address their deepest concerns. In 2020, we added the Irish supplement company Nualtra Limited into the Group. Nualtra offers products to improve the quality of life of people with dietary restrictions due to illness and seniors with nutritional deficiencies due to aging by offering medical foods that efficiently deliver nutrients with minimal burden on the body. By deepening our relationships and engaging in close dialogue with pharmaceutical firms and other companies, research institutions in related fields, and customers using our products, we are continuing to develop and hone the strengths of "AminoScience." We are building out our portfolio of companies and our range of expertise to pursue innovation and prime our ability to address future issues in the healthcare field.

Healthcare

Contract oligonucleotide therapeutics business The AJIPHASE® breakthrough

The Medium-Term ASV Initiatives 2030 Roadmap aims for the AminoScience business to be generating business profits at the same level as the food products business by 2030. The Bio-Pharma Services business will play a key role in our growth strategy for the AminoScience business.

Why the Ajinomoto Group is positioned to contribute to a new era of medical care

The Bio-Pharma Services business has been attracting attention in recent years as a rapidly growing business utilizing “AminoScience,” which is being led by our AJIPHASE®. Our Bio-Pharma Services manufacture oligonucleotide compounds that pharmaceutical manufacturers use to produce oligonucleotide therapeutics.

Broadly speaking, there are three types of drugs: small, medium, and large molecule drugs. Most conventional medicinal therapeutics are small molecule drugs with low molecular weight. Large molecule drugs, or biologics, are composed of proteins with large molecular weight. Antibody therapeutics, such as the Opdivo cancer therapy, are a type of large molecule drug. Currently, medium molecule drugs are receiving attention. The oligonucleotide compounds that the Ajinomoto Group manufactures are gaining recognition as a promising third type of medical modality. The oligonucleotide compounds that are the main component of oligonucleotide therapeutics can be produced through chemical synthesis, which reduces manufacturing cost, and offer high target specificity, therefore causing minimal side effects. Oligonucleotide therapeutics are being used to treat hereditary and cardiovascular diseases, which have been particularly difficult to treat, and offer new avenues for treating cancer and viral infections.

Features of oligonucleotide therapeutics

	Small molecule drugs	Nucleic acid drugs	Large molecule drugs
Manufacturing method (cost)	○ Chemical synthesis (low)	○ Chemical synthesis (low)	Biofabrication (high)
Intracellular targeting	○ Yes	○ Yes	No
Intracellular RNA targeting	No	○ Yes	No
Target molecule specificity	Low	◎ Even higher	○ High
Side effects	Many	○ Few	○ Few
Medicinal efficacy	Low	○ High	○ High

Partially processed by our company based on “The World Middle Molecule Drug Market” (TPS)

Market environment change from 2016 to 2022

Number of approved nucleic acid drugs: 5 ▸ 16 (3 times)

Number of clinical trials of nucleic acid drugs: Approx. 300 ▸ Approx. 700 (2 times)

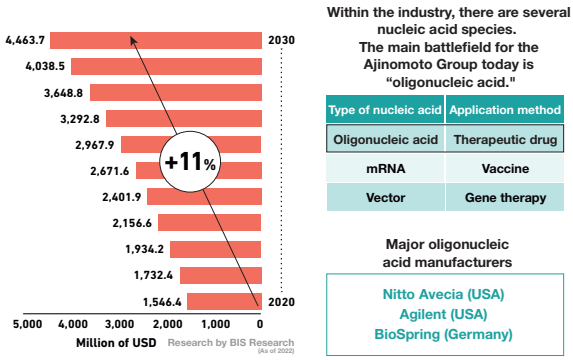
A comparison of the features of small, medium, and large molecule drugs for oligonucleotide therapeutics. Oligonucleotide therapeutics are characterized by higher specificity for target molecules and fewer side effects compared to conventional small molecule drugs.

AJIPHASE®—the world’s only combined solid- and liquid-phase synthesis technology

The oligonucleotide therapeutic market is currently growing at an annual pace of around 11% and is expected to reach a market size of ¥450 billion by 2030 (see Oligonucleotide compounds CDMO market). Markets with such growth promise usually lead to intense pricing competition that reduces profit margins. However, our AJIPHASE® contract manufacturing service for olionucleotide compounds uses a unique liquid-phase synthesis method which will allow us to offer price competitive services while maintaining a high profit margin.

The most common method used to produce olionucleotide compounds is solid-phase synthesis. Although used

Nucleic acid drug CDMO market



Within the industry, there are several nucleic acid species. The main battlefield for the Ajinomoto Group today is "oligonucleic acid."

Type of nucleic acid	Application method
Oligonucleic acid	Therapeutic drug
mRNA	Vaccine
Vector	Gene therapy

Major oligonucleic acid manufacturers

Nitto Avecia (USA)
Agilent (USA)
BioSpring (Germany)

The nucleic acid drug industry is in an overall growth stage, and the CDMO market for nucleic acid drugs is expected to grow to ¥450 billion in 2030. / Manufacturing contracts tend to go to the small number of leading CDMOs. Key to competitiveness will be unique strengths and differentiation.

worldwide, the method requires an expensive dedicated synthesizer and uses a large volume of organic solvents and raw materials to produce only a relatively small amount of deliverables. Although the process is relatively short, it can only synthesize small amounts at one time. This makes solid-phase synthesis adequate for small-lot synthesis for reagent products but not suitable for mass production of final products.

The liquid-phase synthesis method developed by the Ajinomoto Group has essentially the opposite characteristics. Liquid-phase synthesis uses less organic solvents and raw materials and the process speed is slower but industrial-scale mass production is possible with a single synthesis. In addition, the process allows for quality analysis to be performed during synthesis, which enables the formulation of high-quality processes. The most efficient manufacturing process would therefore be a combination that takes advantage of both processes—solid-phase synthesis to produce small volumes at the reagent step followed by liquid-state synthesis for mass production of the finalized product. The Ajinomoto Group provides the world's only oligonucleic compound contract manufacturing service that combines solid- and liquid-phase synthesis, and our manufacturing structure enables us to handle any level of volume from micrograms to tons.

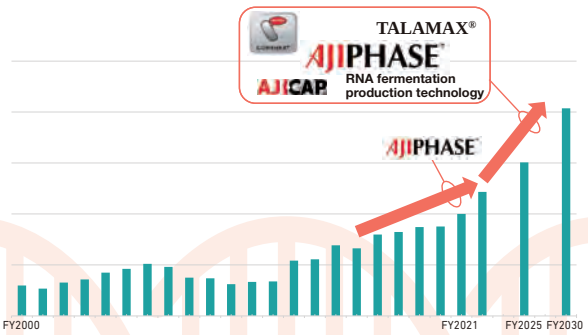
In addition to reducing manufacturing costs, AJIPHASE® also allows companies to use its standard small molecule synthesis facilities with minimal capital investment. The Tokai Plant has converted from manufacturing small molecule active pharmaceutical ingredients (APIs) to liquid-phase manufacturing of medium molecule APIs. Another advantage of liquid-phase synthesis is that it allows for collaboration among companies, and we have already started working with new partner companies. We are also tightening our collaboration with YMC Co., Ltd. for purification.

We are strengthening our production structure using the liquid-phase synthesis method to develop it into a CDMO business.

Our primary method for fortifying our infrastructure has been through capital investment, such as with the acquisition of GeneDesign or by improving our business sites. As we work toward our objectives for 2030, we will now be focusing on enhancing the high-value-added services unique to the Ajinomoto Group to fortify the advantages we have over rival firms. One major aspect of this will be transforming from a contract manufacturing organization (CMO) to a contract development and manufacturing organization (CDMO).

We are continuing to develop the AJIPHASE® technology for the new era of nucleic acid medicine and steadily growing market demand by expanding our manufacturing capacity, introducing new technologies such as hybrid manufacturing methods using enzymes, and creating a unified global marketing team to strengthen our marketing structure.

Image of sales expansion of the Bio-Pharma Services business

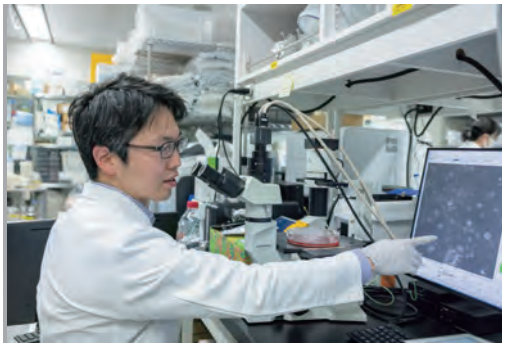


The progress made in the expansion of the Bio-Pharma Services business is remarkable. We will strengthen our AJIPHASE® and other unique manufacturing technologies and solution capabilities to boost sales and accelerate our profit growth.

Healthcare

Strength of the Ajinomoto Group in culture media for regenerative medicine

Regenerative medicine is anticipated to become a groundbreaking area of medical treatment in the 21st century, with research and development of culture media being one of the most important issues in this field. The Ajinomoto Group contributes to this research and development.



Two leading medical experts in cutting-edge cardiac regenerative medicine talk about contribution of the Ajinomoto Group and their expectations for the future

Dr. Keiichi Fukuda is CEO and Representative Director of Heartseed, Inc., a company whose mission is to open the door to the treatment of heart disease through regenerative medicine. He began research into myocardial regeneration in 1995 while working at Keio University Hospital. During his research, Dr. Fukuda successfully differentiated cardiac muscle cells from bone marrow, going on to achieve further success by creating cardiomyocytes from iPS cells, and focusing on the potential of medical culture media (cell culturing media), he presented his findings at an academic conference. “Mr. Okamoto, a researcher from the Ajinomoto Group, attended that conference, and was interested in my work. Cell culture medium contains a great many amino acids, and the Ajinomoto Group had a wealth of knowledge gained from research in this area. Discussions with Mr. Okamoto convinced me that it would be possible to promote growth at every stage of cultivation of cardiomyocytes from iPS cells by putting careful thought into the culture medium, and I decided to move ahead with my research in concert with the Ajinomoto Group.” (Fukuda)

At the time, almost all of the cell culture media used in research and development in regenerative medicine was general material, and no attention was paid to its composition. Dr. Fukuda and the Ajinomoto Group began research and development on cell culture media. “The great thing about the Ajinomoto Group is its ability to analyze the composition of cell culture media. For example, analyzing compositional changes in the culture medium before and after cell culture was an extremely effective way of finding an optimal solution. I was also impressed by the Ajinomoto Group’s deep understanding of research in areas that require a high level of safety, such as myocardial regeneration, and by the generosity they showed by not being willing to settle for overly quick results.

Dr. Fukuda established Heartseed, Inc., in 2015, and is dedicated to research and development intended to improve efficiency and lower the cost of cardiomyocytes derived from iPS cells.

The current status of cardiac regenerative medicine, and our contribution to the development of culture media

Dr. Shugo Tohyama led the research and development of culture media for many years under Dr. Fukuda and has now taken up the mantle of research into cardiac regenerative medicine. “We have been working with the Ajinomoto Group since 2011 to develop culture media, in order to use this media in clinical applications. Thanks to the Company’s huge library of amino acids, we were able to develop a deeper understanding of cellular metabolic characteristics and greatly accelerate our efforts. I’m certain that had we been working on our own, we would have been lagging far behind the stage we have now reached.

Here is an example of joint development of a purification process, which had proved to be a difficult task when creating cardiomyocytes from iPS cells. To create cardiomyocytes from iPS cells, we proliferate large numbers of undifferentiated iPS cells, which are then differentiated to create cardiomyocytes. These cardiomyocytes are then purified and matured to create cardiomyocytes for transplantation. The difficult part of this process was purification. This requires elimination of any iPS cells that do not become cardiac myocytes after differentiation. After searching for difference in amino acids that these two types of cells like to eat, we identified glutamine. We then found that although iPS cells die in a short time if glutamine and glucose are removed from the culture medium, the cardiomyocytes would survive and produce energy if lactic acid was added. “When we were developing this method of purification, the Ajinomoto Group contributed a great deal by providing a variety of culture media with certain types of amino acids removed and by analyzing the culture media itself. “In the course of developing multiple different types of culture media, we had discussions with the researchers at the Company almost every month on which elements could be adjusted to create even better media. We would sometimes make requests, or the Company might offer suggestions; it was a two-way dialogue that was extremely useful in research and development.” (Tohyama)

Research and development in culture media development is still in its infancy. There must be culture media that are perfect for other organ cells than cardiomyocytes, so this is a field with great hidden potential.

Phases of cardiomyocytes

Proliferation
Proliferation of iPS cells in an undifferentiated state. Adding the amino acid tryptophan to the culture improves efficiency.

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Induction of differentiation
iPS cells differentiate to form cardiomyocytes. This is difficult because even slight environmental changes may induce errors in reproducibility. Content not released.

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Purification
Elimination of iPS cells that were unable to differentiate. Work to bring cardiomyocyte purity as close to 100% as possible.

↓

Maturation
The cardiomyocytes created are in the same state as that of a newborn infant. Culture medium to promote maturation in development.

The people we talked to

Keiichi Fukuda

CEO and Representative Director of Heartseed, Inc.

M.D., PhD. Engaged in research in cardiac regeneration from the 1990s, and in 1999 was the first person in the world to create cardiomyocytes from adult stem cells. In 2015, established Heartseed, Inc., a leading company in regenerative medicine.

Shugo Tohyama

Assistant Professor, Department of Cardiology, Keio University School of Medicine / Principal Investigator, Kanagawa Institute of Industrial Science and Technology (KISTEC)

M.D., PhD. Began research into cardiac regenerative medicine under Dr. Fukuda. Developed the world’s first myocardinal sorting method using culture medium and has published many articles on technical development in regenerative medicine.