NKCL·M
NKCL MASTER

White Paper

PERSONALIZED
IMMUNE CARE
PLATFORM

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1. Introduction Background

1.1 Birth / Death

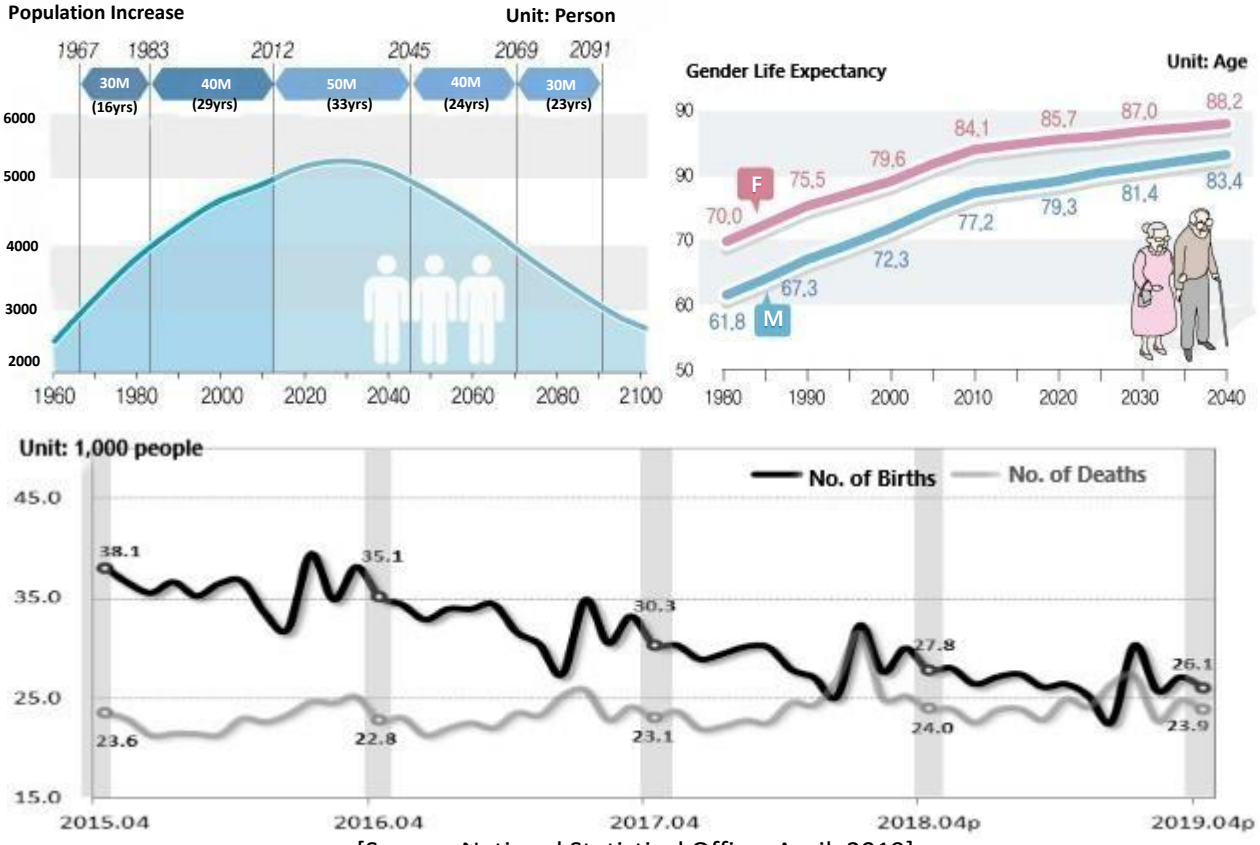
As of the end of December 2017, the world's population is about 7.6 billion. The population began to increase due to the increase in human productivity. After the industrial revolution in the 18th century, the population began to increase rapidly due to the development of medicine and agriculture. Population growth is categorized into three stages, according to the view of Thompson, an American demographer.

Stage 1: Natural state where mortality and birth rate are not artificially controlled

Stage 2: Mortality and birth rate begin to decline, especially with mortality rate rapidly decreasing

Stage 3: Mortality and birth rate both being low

In the case of Korea, total fertility rate in 2017 was only 1.05, which resulted the population decline to be moved forward by 4 years, being 2028. Given the trend of 0.95 total fertility rates for the third quarter of 2018, the National Statistical Office anticipated that the natural decline and population cliff will begin in 2019.

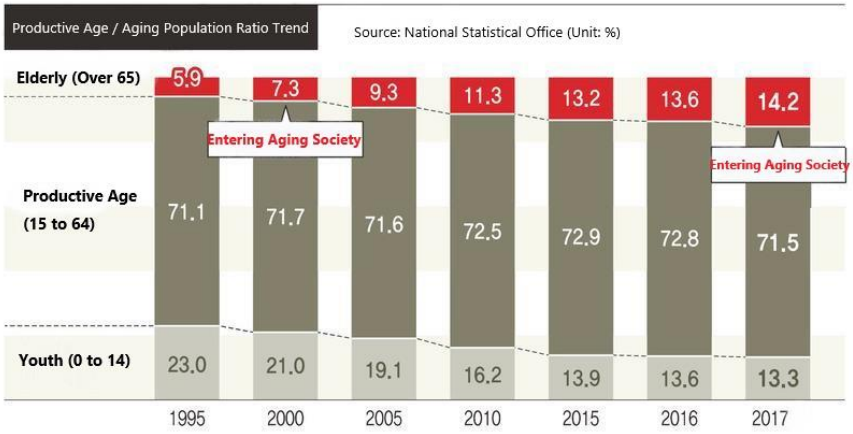


[Source: National Statistical Office, April, 2019]

As of April 2019, the number of babies born was 26,100, down 6.1% from the same month last year, and the number of deaths was 23,900, down 0.4% from the same month. The decrease in the number of births is a major cause of population cliffs, and the decrease in the number of deaths means an

increase in the elderly population.

In addition, as low birth rates and aging populations intensify, in 2017, we will enter an aging society of the elderly exceeding 14% of the total population. The point at which it exceeds 20% is called the "old age society", and we are expected to enter the "old age" by 2026. The direct cause of aging society is anticipated to be life growth due to medical development rather than childbirth.



[Source: National Statistical Office, Aging Population Ratio Trend]

The body's immunity is reduced by age and disease. About 5,000 mutant (cancer) cells occur every day. Normal people do not develop cancer by the action of immune cells (immune system), but when their immunity weakens, they are exposed to cancer or disease.

The number of cancer patients (survivors during treatment or post-treatment) reached about 1.74 million from 1999 to 2016, when cancer statistics were started to be calculated nationwide, and this means 1 in 29 people are cancer patients. In particular, among elderly over the age of 65, 1 in 9 patients were cancer patients, 1 in 7 men and 1 in 12 women. By carcinoma, the number of patients with thyroid cancer was the highest, followed by stomach cancer, colon cancer, breast cancer, prostate cancer, and lung cancer.

The dream of prolonging life has been in the past or present and for all, and now, with the power of medicine, it is fulfilling little by little. At present, the causes of death of human beings (cause of death) are very diverse, but when the causes are classified, the proportion of malignant neoplasms (cancer) is increasing. In Korea, as for age-related deaths, cancer ranks first after age 40, followed by cardiovascular disease as second. The mortality rate from cancer is also high, which will lead to higher medical treatment rates for common diseases that will cause cancer to become even more predominant.

(Unit: per 100,000 population, %)

	Age 0	Age 1- 9	Age 10-19	Age 20-29	Age 30-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79	Age over 80
1st	Specific conditions originating before and after childbirth	Malignant neoplasm	Intentional self-harm (suicide)	Intentional self-harm (suicide)	Intentional self-harm (suicide)	Malignant neoplasm	Malignant neoplasm	Malignant neoplasm	Malignant neoplasm	Malignant neoplasm
2nd	Congenital malformations and chromosomal abnormalities	Transportation accident	Transportation accident	Transportation accident	Malignant neoplasm	Intentional self-harm (suicide)	Intentional self-harm (suicide)	Heart disease	Heart disease	Heart disease
3rd	Sudden Infant Death Syndrome	Congenital malformations and chromosomal abnormalities	Malignant neoplasm	Malignant neoplasm	Transportation accident	Liver disease	Heart disease	Cerebrovascular disease	Cerebrovascular disease	Pneumonia
4th	Heart disease	Assault (homicide)	Heart disease	Heart disease	Heart disease	Heart disease	Liver disease	Intentional self-harm (suicide)	Pneumonia	Cerebrovascular disease
5th	Assault (homicide)	Heart disease	Drowning	Cerebrovascular disease	Liver disease	Cerebrovascular disease	Cerebrovascular disease	Liver disease	Diabetes	Hypertension

[NSO, Age-specific cause of death statistics (malignant neoplasm = cancer): 2015]

In the past, cancer was considered an incurable disease, but with the advancement of medicine, many expect that one day, cancer will be treated like a normal disease. Still, the fear of cancer, the course of treatment and the prognosis of the cancer cannot be said to be good except for a few. Only with the development of preventive medicine, the rate of early detection of cancer is increasing, leading to a higher survival rate.

However, the **cancer mortality** rate is gradually increasing to deaths **per 100,000 population** ('07: 137.5 → '17: **153.9**) with lung cancer mortality ('07: 29.1 → '17: 35.1) being the highest. In 2017, the cancer mortality rate (per 100,000 population) was highest in the order of lung cancer (35.1), liver cancer (20.9), colon cancer (17.1), and stomach cancer (15.7). What is unusual here is that **the incidence of cancer increases proportionally with the aging of the population**.

* Acute Myeloid Leukemia Disease
(1) No. 1 cancer incidence for age 1-14 years, 3.9 per 100,000 population (National Cancer Center 2013) (2) Low survival rate: over 90% deaths (1,666 people, National Cancer Center 2012)
* Lung Cancer Disease
(1) Ranked 1st at 22.8% (17,440 deaths) by total cancer type (National Cancer Center 2014) (2) Low survival rate of 10% within 5 years

It is estimated that the number of cases of disease is estimated at 1.174 million from 1999 to 2016, when **229,000 new cancer patients occurred every year** and national cancer occurrence statistics started to be calculated.

As the number of cancer patients increases, we can see a lot of cancer patients around us, and the prevention and treatment of cancer has become one of the main concerns. In particular, in terms of treatment, there are traditional protocols prepared by hospitals and the medical community, but unlike other diseases, it is almost impossible to be 100% cured by this protocol. In the case of terminal cancer patients, there is no such treatment, so they focus on palliative treatment or travel overseas with hopes of new cancer treatment.

Thus, among the currently available therapies, cell therapy products with the least side effects and high treatment rates are emerging as the biggest issues. This is a regenerative medicine field, and the revision of related laws has emerged as a very hot potato.

1.2 Regenerative Medicine

Regenerative medicine is a cutting-edge convergence technology field that helps function to be restored by replacing or regenerating a damaged cell or tissue due to disease, accident or aging. The National Institutes of Health defines regenerative medicine as follows.

A new field that will revolutionize how to improve health and quality of life by maintaining, restoring and promoting the functioning of tissues and organs through the convergence of biology, pharmacy and engineering

This regenerative medicine is the beginning of a whole new technology against disease, and the expectation for regenerative medicine is so great that it is reported that human beings are new human beings with regenerative medicine and stem cells unlike the past. The field also ranges from refractory diseases without proper treatment to cosmetology such as anti-aging, and there is a great expectation for the creation of economic added value.

In addition, regenerative medicine is expected to continue its **high growth focus on cell therapies**. Regenerative medicine is largely divided into **cell therapy, tissue engineering, and biomaterials**, and cell therapy is expected to make the most significant progress.

1.3 Advanced Regenerative Medicine Law and Regulation Trends

The healthcare paradigm is rapidly shifting from Healthcare 1.0, which aims for life-saving to Healthcare 2.0, which aims to control symptoms and disease management, and then to Healthcare 3.0, which aims to cure and prevent.

This was made possible by technological innovations in the fields of cell, genetic engineering, and IT convergence and it can be seen as the result of market demand such as extending the life span and reducing medical expenses.

Another change is that desperate patients are willing to move across borders to other countries where treatment is possible for advanced treatments that are not possible in their laws or in the medical delivery system. One example is “stem cell tourism”, which travels directly to countries where stem cell treatment is possible. This is a commercial practice that promotes the efficacy of unlicensed treatment online or

directly to patients, and in developed countries there is a great concern about the safety problems and economic losses that can occur in their patients. Korea is not free on this matter either. In addition to these backgrounds, the industrial value of these future medicines has led to the rapid development of laws and systems in the field of regenerative medicine in advanced countries.

The U.S. has been applying a rapid license since December 2016 for 'Regenerative Advanced Therapies' as a solution to serious diseases not treated by the 21st Century Cures Act.

Subsequently, the US FDA issued new guidelines (two drafts and two final) to accelerate approval of Regenerative Medicine Advanced Therapy (RMAT) in November 2017, accelerating approval of new treatments while increasing safety surveillance of unproven treatments.

In Europe, a separate regulation (Regulation No 1394/2007) has been in force for high-tech medical products since December 2018. Advanced Therapy Medicinal Products (ATMPs) in Europe include cell therapies, gene therapy, tissue engineering therapies, and combination high-tech medical products.

In China, regulation, which was halted in 2016 due to cell therapy deaths (Restrictions on the sale of unapproved cell therapies after the death of a rare cancer patient - Wei Zexi who died during an unapproved cell therapy in 2016) was approved and opened new avenues for cell therapy in March 2019 with the guideline for the sale and medical practice of untreated cell therapies in more than 1,400 excellent hospitals (Grade 3A Hospitals), which provide specialist medical and medical research published by the Ministry of Health.

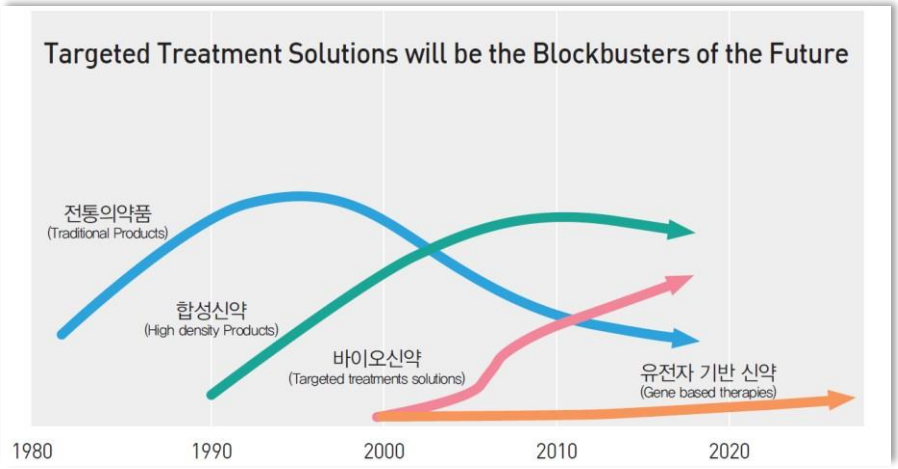
China is also striving to become the world leader in all areas by presenting ‘Made in China 2025’**.** In particular, the bio and medical industry, among the top 10 core fostering industries, is expected to grow to a maximum of 10 trillion yuan by 2020, and has shown rapid movements such as applying for new drug approvals and simplifying clinical procedures since mid-2016. In addition, one-third of the more than 6,000 people (as of the end of 2017) who returned to China through the Thousand Talents Program a program to attract high-quality foreign talents from China, are highly regarded nationally as they are excellent scientists in bio and medicine fields (China's high-tech R & D staff of biotechnology field is around 40,000).

The bio industry in China has maintained an annual average growth rate of more than 15% since 2010, and it is projected that the bio industry will grow from 8 trillion to 10 trillion yuan (1300 trillion to 1600 trillion won) by 2020.

Japan, like Korea, is required to receive approval for treatment through clinical system under the Pharmacist Act., however is the difference is that Japan has already enacted Regenerative Medicine Act (In accordance with the 'Regenerative Medicine Safety Act (Regenerative Medicine Act)’ announced in 2015, the license is divided into research and treatment purposes separately from the drug approval process through the Pharmacist Act.), which gave doctors a lot of discretion apart from the Pharmacist Act. In the case of Japan, it can be said that it is intended to lead the industry in cell therapy, including stem cells. Also in Korea, there are a bill on the support and management of advanced regenerative medicine, proposed by Saenuri Party Rep. Seunghee Kim (10 initiatives, May 2016), “Advanced Regenerative Medicine Act” proposed by Democratic Party of Korea Rep. Hyesook Jeon (12 initiatives, November 2016), and “Legislation on Advanced Regenerative Medicine and Advanced Biologics” proposed by Liberty Korea Party Rep. Myungsoo Lee (August 2018).

The reason why Pharmacist Act, FDA, etc. are mentioned is because once culture for cell therapy starts (usually there are not many collected cells, so it is necessary to culture them for normal cell treatment), it is considered as a drug, and thus, a clinical trial following the new drug development process should be performed. The FDA has the relevant regulatory rights (Article 16 of the Advanced Regenerative Medicine Act states that where a human cell is extracted, inspected, cultured, processed or stored and provided to regenerative medical institutions, it is required to have appropriate facilities, personnel and equipment as prescribed by Presidential Decree, and to be authorized as an advanced regenerative medical cell processing facility by the Director of the Ministry of Food and Drug Safety), and if the regenerative medicine law is redefined, such areas become more freed.

1.4 Pharmaceutical Industry



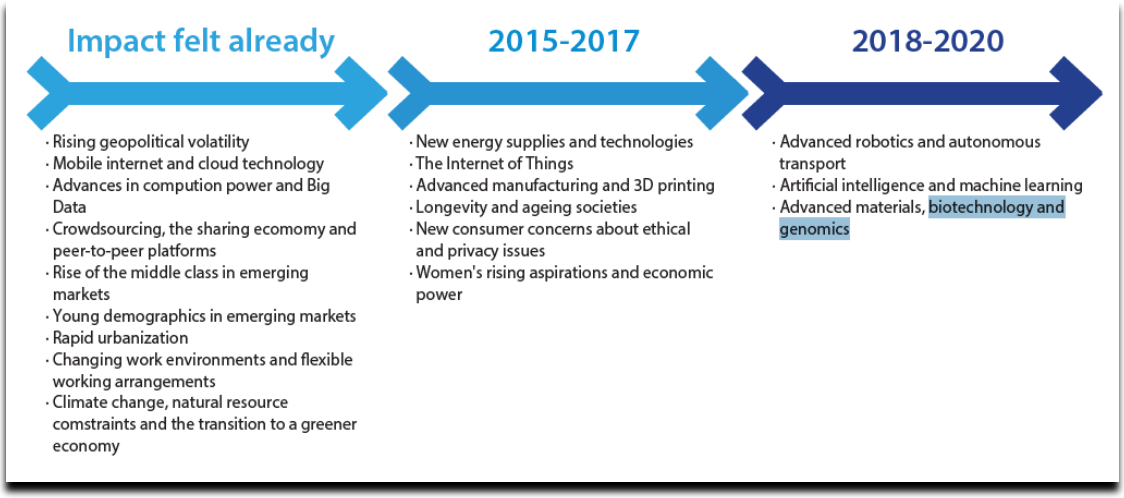
[Source: IBM Pharma 2010: The threshold of innovation]

Starting in the mid-1990s, the global pharmaceutical market is moving toward synthetic and bio-new drugs. This reflects the development of medicine and various technologies. In terms of industry, although the global growth rate of global IT sector was 2.9% between 2013 and 2015, the growth rate of bio side was 9.2%. This flow and biopharmaceuticals have historically been seen in the drug market as traditional drugs, synthetic new drugs, bio new drugs, and gene-based new drugs.

Synthetic Drugs vs. Biopharmaceutical		
Synthetic Drugs 	Classification	 Biopharmaceutical
Manufacture chemical raw materials by chemical synthesis	Manufacturing Method	Manufactured by culturing bio-derived substances (antibodies, cells, etc.)
Mainly Tablet	Format	Mainly Injection
Low cost due to mass production with standardized manufacturing method	Manufacturing Cost	Complex bio production facilities required and high cost
High efficacy for routine disease, standard treatment	Characteristic	High therapeutic effect such as rare and intractable diseases

[Source: Ministry of Science, ICT and Future Planning: Bio Future Strategy]

Especially in the 2000s, research on bio- and gene-based drugs has been actively conducted, which seems to be more motivating since the therapeutic effect is higher than that of conventional drugs for refractory disease treatment.



[Source: Future of jobs survey, World Economic Forum (January 2016)]

These global trends presented the trends of the fourth industrial revolution in the Davos Forum in 2016, showing that new conceptual medicine fields such as biotechnology and genetics are emerging from 2018 to 2020.

Such trends are also active in the field of investment in the industry.

Field	2011	2012	2013	2014	2015	2016.05
ICT Manufacturing	1754	2099	2955	1951	1463	351
ICT Service	892	918	1553	1913	4019	1266
Electricity/ Machine/ Equipment	2066	2433	2297	1560	1620	728
Chemical/ Material	1266	1395	989	827	1486	600
Bio / Medical	933	1052	1463	2928	3170	1352
Video/ Concert/ Record	2083	2360	1963	2790	2706	840
Game	1017	1126	940	1762	1683	485
Distribution Service	1270	608	1092	2046	3043	995
Others	427	342	593	616	1668	401
Total	**12608**	**12333**	**13845**	**16393**	**20858**	**7018**

[Source: the bell, Investment Ratio by Business Type of Startup Investment Association]

In Korea alone, this phenomenon is remarkable even in the case of start-up investment. As of 2014, the highest investment in a single sector is taking place in the bio / medical sector.

Year	Market Size (YOY Growth Rate)
2012	19,832(22.6%)
2013	22,283(12.4%)
2014	19,849(△10.9%)
2015	16,406(△17.3%)
2016	18,308(11.6%)

[Source: Ministry of Food and Drug Safety, 2017.7, Domestic Biopharmaceutical Market Size]

In terms of sales, as shown in the table below, the biopharmaceutical market amounted to about 1.8308 trillion in 2016, growing 11.6% compared to 2015 and in terms of trade balance, the most surplus was recorded in the last five years.

The position of biopharmaceuticals in pharmaceuticals can be confirmed through the fact that biopharmaceuticals account for 52% of the world's top 100 pharmaceuticals. According to the **Nature 2014**, **60% of advanced cancer patients will receive chemoimmunotherapy**, which can be expected to be very active in both scientific and commercial terms.

Looking at the current cancer drug market, we can see the growth of the anticancer drug market as shown below.

	Drug Name	Generic Name	Company Name	2013	2014	2015	2016	2017	2022 (F)
1	Revlimid	lenalidomide	Celgene	4,280	4,980	5,801	6,974	8,187	14,072
2	MabThera/Rituxan	rituximab	Hoffmann-La Roche	7,497	7,545	7,323	7,412	7,505	3,259
3	Herceptin	trastuzumab	Hoffmann-La Roche	6,556	6,861	6,796	6,886	7,125	3,428
4	Avastin	bevacizumab	Hoffmann-La Roche	6,745	7,016	6,948	6,887	6,794	3,853
5	Opdivo	nivolumab	Bristol-Myers Squibb	-	6	942	3,774	4,948	8,775
6	Keytruda	pembrolizumab	Merck & Co	-	55	566	1,402	3,809	11,149
7	Ibrance	palbociclib	Pfizer	-	-	723	2,135	3,126	7,229
8	Xtandi	enzalutamide	Astellas	579	1,331	2,244	2,244	2,619	4,110
9	Zytiga	abiraterone acetate	Johnson & Johnson	1,698	2,237	2,231	2,260	2,505	1,526
10	Perjeta	pertuzumab	Hoffmann-La Roche	352	1,004	1,502	1,874	2,231	4,873
11	Imbruvica	ibrutinib	AbbVie	-	-	659	1,580	2,144	4,636
12	Alimta	pemetrexed disodium	Eli Lilly	2,703	2,792	2,493	2,283	2,063	945
13	Sprycel	dasatinib	Bristol-Myers Squibb	1,280	1,493	1,620	1,824	2,005	783
14	Gleevec/Glivec	imatinib mesylate	Novartis	4,693	4,746	4,658	3,323	1,943	398
15	Imbruvica	ibrutinib	Johnson & Johnson	-	200	689	1,251	1,893	5,210
16	Tasigna	nilotinib	Novartis	1,266	1,529	1,632	1,739	1,841	2,214
17	Pomalyst /Imnovid	pomalidomide	Celgene	305	680	983	1,311	1,614	2,985
18	Xgeva	denosumab	Amgen	1,019	1,221	1,405	1,529	1,575	2,144
19	Afinitor/Votubia	everolimus	Novartis	1,309	1,575	1,607	1,516	1,525	308
20	Velcade	bortezomib	Takeda	1,392	1,481	1,442	1,225	1,291	129

[Source: Globaldata, Top 20 worldwide anticancer drug sales: Unit USD 1M]

Revlimid, the world's No. 1 company, is forecasting a **single company's anticancer drug sales of 18 trillion won**. This will include sales of cell and gene therapies in addition to the existing anticancer market, and as the growth potential for cell therapies is expected compared to the past growth, the proportion of cell therapies in the sales of anticancer drugs is expected to be high.

Ranking	Anticancer drugs	Ingredient Name	Manufacturer	2013	2014	2015	2016	2017
1	AVASTIN	Bevacizumab	Roche	161	260	495	806	920
2	HERCEPTIN	Trastuzumab	Roche	863	930	1008	1,034	840
3	GLIVEC	Imatinib	Novartis	827	531	456	482	484
4	ELOXATIN	Oxaliplatin	Sanofi	339	307	NA	349	416
5	ERBITUX	Cetuximab	Merck	78	231	362	394	400
6	XALKORI	Crizotinib	Pfizer	30	45	118	272	365
7	REVLIMID	Lenalidomide	Celgene	0	118	272	290	353
8	MABTHERA	Rituximab	Roche	295	332	357	372	313
9	GEMZAR	Gemsitabin	Eli Lilly	278	284	293	285	312
10	TASIGNA	Nilotinib	Novartis	119	154	215	278	308
11	ALIMTA	Pemetrexed	Eli Lilly	445	484	419	318	306
12	IRESSA	Gefitinib	AstraZeneca	295	295	307	295	242
13	SPRYCEL	Dasatinib	BMS	135	161	202	225	234
14	NEXAVAR	Sorafenib	Baeyer	225	205	208	210	216
15	TAXOTERE1	Docetaxel	Sanofi	198	187	186	170	204
16	VELCADE	Bortezomib	Ansen	221	224	258	233	200
17	AFINITOR	Everolimus	Novartis	61	116	180	191	195
18	XAKAVI	Ruxolitinib	Novartis	NA	NA	70	131	185
19	OPDIVO	Nivolumab	BMS	0	0	1	67	125
20	KEYTRUDA	Pembrolizumab	MSD	0	0	19	110	122

[Source: IMS, Top 20 domestic anticancer drug sales, Unit KRW 100M]

In the domestic anticancer drug market, sales are about 1/100 of the world, and most of them are imported from overseas.

Anticancer drugs are **the most imported drugs** in Korea. Considering the expansion of the anticancer drug market due to the increase in the number of cancer patients, if the development and production of new anticancer drugs is not made in Korea, foreign dependence of anticancer drugs will be intensified in the future.

> In terms of imports of medicines from the KFDA survey, anticancer drugs ranked first in the group of drugs and exceeded 450 billion won, mainly importing drugs from large multinational pharmaceutical companies such as Roche, Novartis, AstraZeneca, and Eli Lilly. By item, 6 of the top 30 species were included, and Roche's Herceptin Inj. 150mg is the highest income among anticancer drugs.

Classification	Genetically engineered proteins	Cell therapy	Gene therapy	Biological agents	
				Blood products	Vaccine
Active ingredients	Peptide or Protein Manufactured Using Genetic Engineering	Live cells cultured, expanded, screened, and manipulated in vitro	Genetic material for the purpose of treating diseases	Blood component medicine and blood fraction medicine using blood as raw material	Proteins or microorganisms aimed at preventing infectious diseases
Domestic market size (ratio)	551.6M won	10.7B won	-	457.6M won	711M won
Type	Growth hormone, insulin, anticancer drugs, autoimmune drugs	Somatic cell therapy, stem cell therapy	DNA vaccine	Red blood cells, platelets, plasma, albumin, etc.	Influenza vaccine, pneumococcal vaccine
Related companies	Green Cross, Celltrion, Samsung Bioepis	Medipost, Kolon Life Science, Pharmicell	Helixmith, Genexine	Green Cross, SK Chemicals	Green Cross, SK Chemicals, LG Life Science, Ilyang

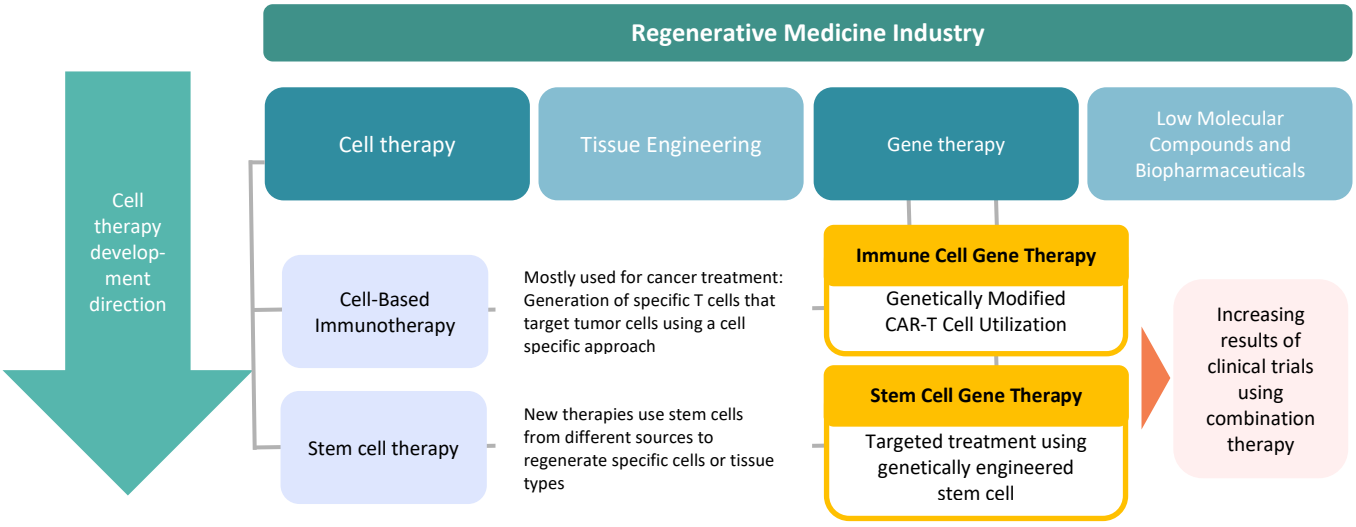
[Source: Korea Biopharmaceutical Association: Domestic Status of Biopharmaceuticals]

The proportion of cell therapies in the domestic market is small at 0.1%. This means that the growth potential is high even considering global research and market trends. In the coming years, the proportion will increase dramatically, which means that the domestic market will grow and diversify. In addition, stem cells and somatic cell therapy products have a high proportion, but in terms of side effects and therapeutic effects, it is expected that the proportion of other cell therapy products such as NK cell therapy products will increase.

Year	Synthetic Drugs	Biopharmaceutical					Herbal Medicine
		Total	Genetic recombination	Biological agents	Cell therapy	Gene therapy, etc.	
2014	465	170 (26.0%)	110	29	24	7	18
2015	451	202 (30.0%)	158	14	25	5	21
2016	387	226 (36.0%)	151	33	33	9	15

[Source: Ministry of Food and Drug Safety press release, approval status of clinical trials by sanction]

As of now, the clinical trial approval in Korea is limited to the stem cell side, but it is expected to move to the 'cell-based immunotherapy'.



[Source: Frost & Sullivan, Future of cell therapy in regenerative medicine market (2016.5)]

In addition to the traditional cell therapy market, it is expected that growth will be directed toward cell therapy and gene therapy after clinical trials have been successfully confirmed in terminal cancer patients.

1.5 Blockchain Introduction Background (Introduction of Blockchain for NK Cell Culture)

If blockchain technology is introduced into the bio industry, it can be very useful for efficiently managing and storing human DNA and personal medical data. In the provision of personal medical information, data can be delivered while maintaining the protection of sensitive personal information. By integrating medical data into the blockchain, we can build credible clinical big data, thereby contributing to medical development and opening the way for future generations to treat cancer.

1.6 Background on introducing Brand Token

NKCL Master is the major master coin that act as the center of the NKCL Brand Coins that are issued according to their business fields. NKCL is a Personalized Immune Care Platform. It can be applied in various business areas like anti-cancer, anti-aging, beauty and retail products. In order to overcome the difficulties caused by the differences in these fields, Brand Tokens are issued. Brand Token is used for a limited purpose and it can also be used as a compensation measure according to its business purpose.

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IMMUNITY

2. What Is Immunity?

2.1 Immunity

Immunity refers to the body's defense system that protects our bodies against pathogenic microorganisms such as bacteria and viruses. Immunity in the broad sense protects the body and prevents it from progressing to diseases, including external factors such as pathogens, toxins, and harmful substances, as well as all risks to health, including allergens and abnormally proliferating cancer cells as defense system. In short, it means the body's resistance to external intrusions.

The function of the immune function prevents the invasion of harmful germs or harmful substances and helps to maintain health by finding and removing abnormally modified cells. Inflammation causes swelling, soreness, and fever. This reaction is a sign of abnormality in our body and the result of immune action to prevent the spread of infection.

Immunology, the study of immunity, is a study that brings about the body's defense mechanism against external pathogens. In our case, the immune system is called the immune system. The immune system has the ability to distinguish between self and non-self, and no immune response is induced for itself, but for others. When outside pathogens such as bacteria or viruses enter the body, the immune system detects them and kills them directly or kills cells infected with them.

2.1.1 Types of Immunity

Normally, immunity can be divided into natural immunity, which is innate immunity at birth, and acquired immunity, which is acquired by vaccination or after the disease.

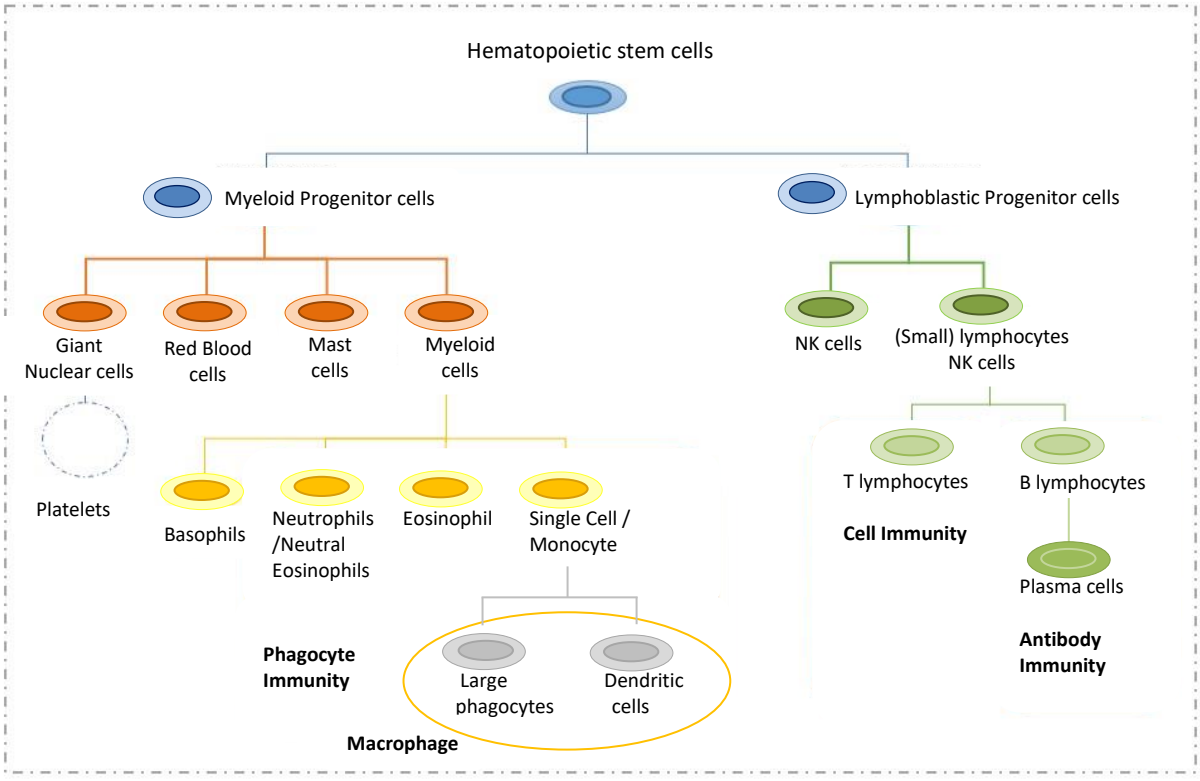
Natural immunity is a primary immune system that responds to any pathogen, including phagocytosis of white blood cells and macrophages that ingest and destroy pathogens from physical barriers such as skin, mucous membranes, saliva, tears, stomach acids, and digestive enzymes.

Acquired immunity remembers the information of a pathogen or antigen that has entered once, and when invaded again, it produces and removes specific antibodies from immune cells such as lymphocytes, or efficiently protects them through immunomodulators such as cytokines. In order to obtain acquired immunity, you must be vaccinated appropriately for your age or epidemic.

2.1.2 Immune System (Immune System Organs and Cells)

Cells in the body's immune system that are responsible for immune function are produced by specific organs, undergo differentiation, and move to each organ in the body to play its role. The immune organs are divided into **primary lymphoid organs** and **secondary lymphoid organs**. In the primary lymphoid organs, immune cells are mainly produced or differentiated, and the place where most of the generated immune cells move and stay is the secondary lymphoid organs. The primary lymphoid organs are the **bone marrow** from which B and T cells are made and the **thymus** from which the differentiation of T cells occurs. The secondary lymphoid organs include various **lymph nodes** located in the corners of the body to respond quickly in the early stages of infection. In other words, Spleen, tonsils, adenoids, Peyer's patches, appendix, etc. belong to the secondary immune organs. (1)

The immune cells of our bodies (NK cells, T cells, B cells, macrophages, etc.) are classified in various ways, and do many things. However, these immune cells are transformed into various cells through immune cell differentiation process starting from hematopoietic stem cells (All immune cells differentiate from hematopoietic stem cells in the bone marrow to largely become lymphoid progenitor cells and myeloid progenitor cells. All immune cells differentiate from hematopoietic stem cells in the bone marrow to largely become lymphoid progenitor cells and myeloid progenitor cells. Lymphoid progenitor cells differentiate into T cells and B cells responsible for acquired immunity, and myeloid progenitor cells differentiate into macrophage, eosinophil, neutrophil, basophils, megakaryocytes, and erythrocytes) to play their respective roles.



[Immune Cell Differentiation]

Macrophages are made from monocytes, as shown in the figure below. These macrophages can produce free radicals that can be sprayed around to kill bacteria, or provide information about foreign substances that have invaded other immune cells by sprinkling external bacterial proteins on their surface (presentation of antigen). In addition, when antigen-antibodies bind to each other, they can be removed by being eaten, the wound can be treated, and the most typical function is phagocytosis.

Phagocytosis of macrophages has a sensor (pattern recognition receptor) that allows macrophages to recognize when bacteria enter. Macrophages themselves do not have very good phagocytic function, but the important thing is that they have these antigen presenting functions and various regulatory functions.

T-lymphocytes are one of the lymphocytes responsible for the origin of adaptive immune immunity. They are named after T cells because they mature in the thymus. About three quarters of all lymphocytes are T cells.

T cells are classified into naive T cells that have not yet met antigen, mature effect T cells (adjuvant T cells, cytotoxic T cells, natural killer T cells), and memory T cells that meet antigen. It is responsible for cell immunity that induces infected cells or cancer cells by apoptosis.

B lymphocytes are the part responsible for humoral immunity that captures antigens that float in blood or lymph fluid with antibodies.

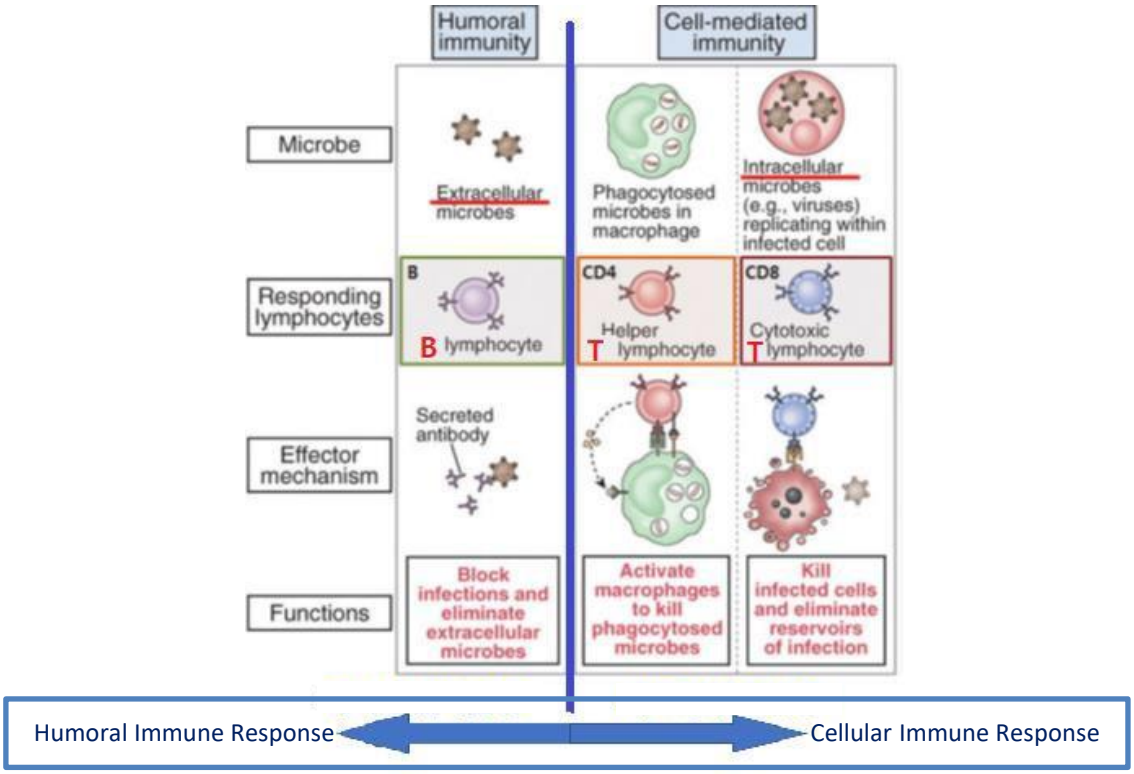
2.1.2.1 Dendritic Cell

B lymphocytes are one of mammalian immune cells known as antigen-transfer cells and are the most potent antigen-transmitter cells in the immune system. It is the only immune cell that has the ability to induce a primary immune response that can stimulate naive T cells that have never been exposed to antigen, and the ability to induce immune memory (It is known that the secretion of various cytokines can induce the generation of antigen-specific killer T cells, proliferation and activation of Th1 cells).

It helps other immune systems deal with pathogens, and in the absence of these cells, rheumatoid arthritis, allergic reactions, and cancer cells develop. Dendritic cells are largely divided into immature dendrites and mature dendritic cells. Both of these cells pass through iDCs and become mDCs with immune-inducing functions and cancer cell recognition.

2.1.2.2 B lymphocytes and T lymphocytes

The first immune response generated after the onset of a pathogen infection is called an innate immune response**. Innate immune responses** are mainly caused by **macrophages** or **dendritic cells** that directly recognize pathogens. The response that occurs to eliminate pathogens that have not been eliminated by the innate immune response or to **suppress the spread of the pathogen infection** is an **acquired immune response**. Cells involved in the acquired immune response are **B lymphocytes** and **T lymphocytes**, and these cells are known to induce humoral immune responses to produce antibodies and cellular immune responses to kill infected cells. Further refinement of cellular immune responses can be divided into CD4 T lymphocytes (helper lymphocytes), which help enhance the function of macrophages or B lymphocytes, and CD8 T lymphocytes (cytotoxic lymphocytes), which induce infectious cell killing.

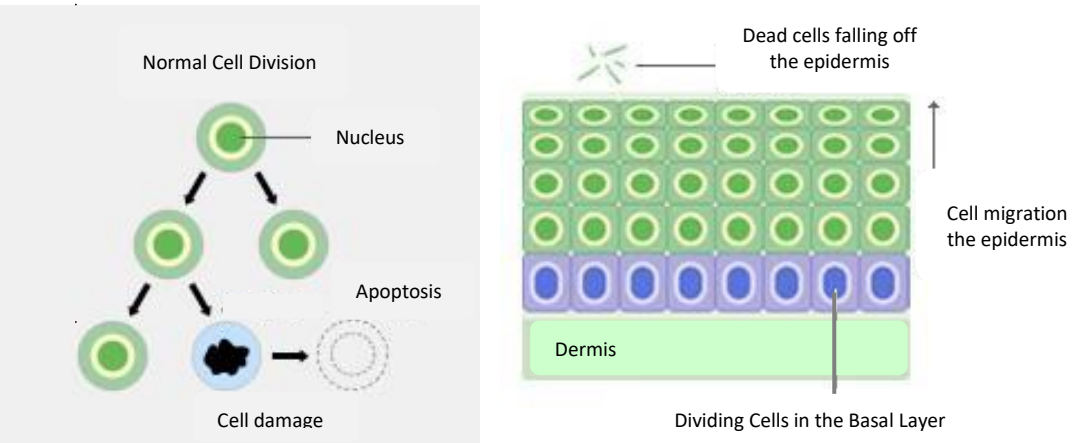


2.1.3 Cancer Cell

Cancer or Malignant tumor (Malignant neoplasm) is **a disease that continues cell division because the cell cycle is not regulated**. In terms of cell division, if a cell is damaged for some reason, it is treated and recovered to act as a normal cell, but if not recovered, it dies on its own. However, when a change occurs in a cell's genes, the cells change abnormally, incompletely mature, and proliferate excessively, which is defined as cancer.

Cancer does not occur in dead tissue without growth, such as hair and nails, but can occur in all other tissues. Incidences vary by tissue. In the case of breast cancer, an incidence of 40% is reported in the upper left and 21% in the lower right.

Cancer is divided into carcinoma and sarcoma according to the site of occurrence. **Carcinoma** refers to malignant tumors from epithelial cells such as mucosa and skin, and **sarcoma** refers to malignant tumors from non-epithelial cells such as muscle, connective tissue, bone, cartilage and blood vessels. When cancer is classified according to the origin of cancer cells, it is divided into 'conjunctival tumor' and 'epithelial tumor'. At this time, the 'sarcoma' suffix is attached to the 'conjunctival tumor (malignant lipoma is called liposarcoma, and the malignant fibroid is called fibrosarcoma), and the epithelial tumor is suffixed as 'carcinoma' (squamous cell carcinoma, adenocarcinoma).

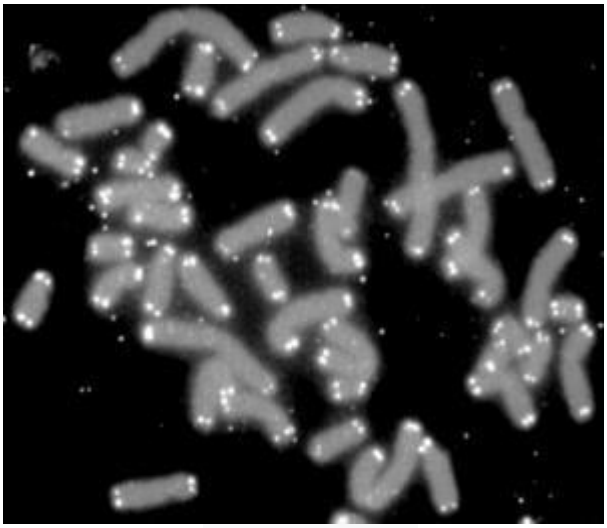


[National Cancer Center: Normal Cell Division]

In normal cells, when the cells are damaged, they are induced by apoptosis and lose their life cycle. In general, cells are not able to divide cells more than a certain number of times. In other words, the cells undergo aging and die. It means that the number of cells is adjusted by newly generated and destroyed.

In 1961, while studying the aging of cells, Dr. Leonard Hayflick found that the number of divisions of cells depends on life and organs, and then the cells age and die. He found out that the cells of the fetus divide about 100 times, and the aged cells divide about 20 to 30 times before aging, and called it **Hayflick Limit**. Cats can divide 8 times, horses 20 times, and humans about 60 times. This is the **telomeres** found later.

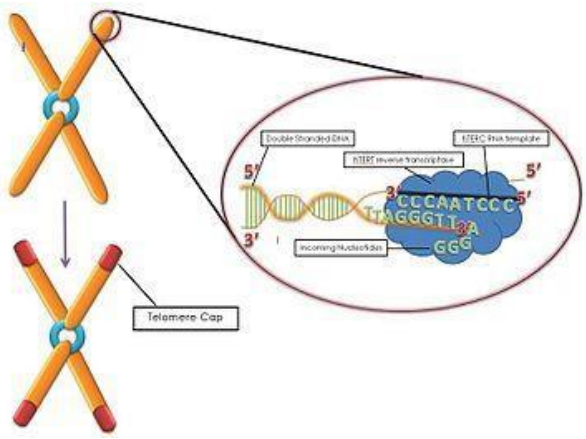
However, this research was known only to a few scientists, so the research was not actively conducted.



Telomere (white) covering the end of the human chromosome (gray)

As you can see in the picture on the left, the telomeres at the end of the chromosome affect their aging by their length.
The length is used as a unit called 'kilobase (unit of nucleic acid chain length such as DNA)'. In humans, the shorter telomeres can lead to aging that prevents cell division.

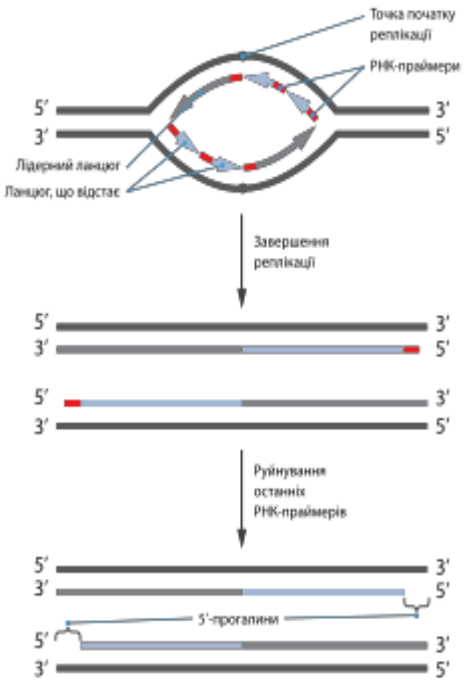
In humans, telomeres repeat six DNA sequences hundreds to thousands of times, and are located at the ends of chromosomes to prevent chromosomal degradation when cells divide.
Each time a cell divides, the telomeres are shortened by the loss of 50 to 200 telomere DNA nucleotides from the chromosome ends.



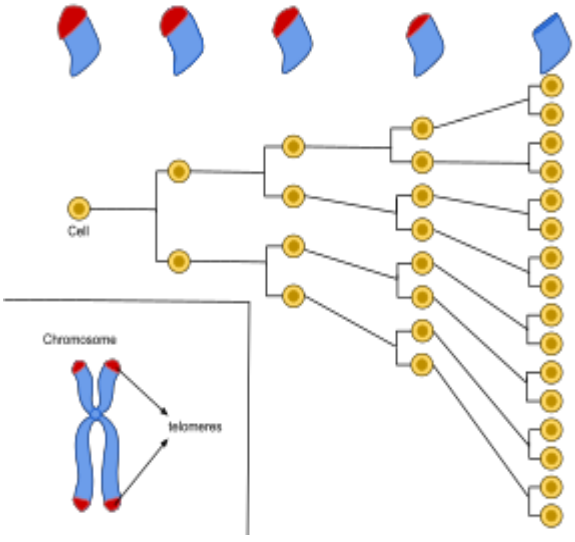
Telomere Protecting Chromosomal Ends

The shorter the telomeres, the older the cells get. After many divisions, if most of the telomere DNA is lost, the cell stops dividing.

A preliminary study conducted at the University of California involved 35 people diagnosed with early prostate cancer and had 10 of them change their lifestyle. Vegetarian diet (fruits, vegetables, grains of untreated chemicals, low fat, refined sugars), moderate exercise (walking for 30 minutes, 6 days a week), stress reduction (yoga stretching, breathing, meditation), and weekly group support was the way. In comparison with the other 25 participants, approximately 10% longer telomeres were observed in the lifestyle change group.



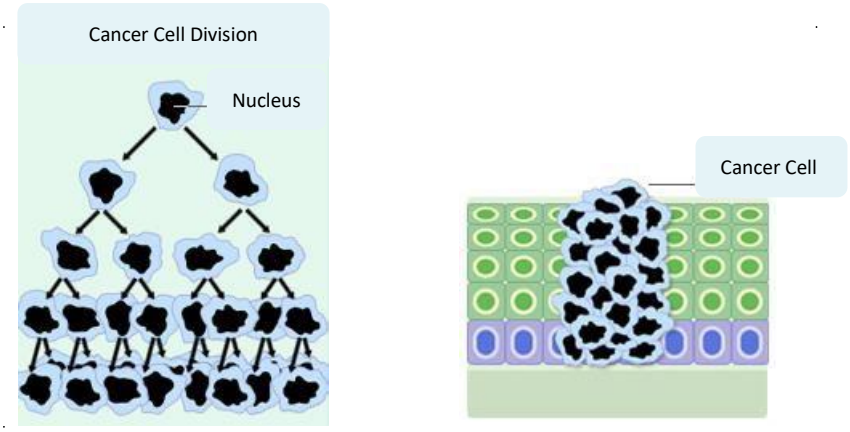
DNA double strands shrinking as they replicate



Hayflix limit: telomeres shrinking as they replicate

It was not until the early 1990s that telomeres were found to be located at the ends of chromosomes by biocytologists. Subsequent studies have revealed the aging mechanism of cells through telomeres.

Unlike the normal cell division process as described above, in the case of cancer cells, if the gene of the cell changes due to various reasons, the cells abnormally change, incompletely mature, and proliferate excessively. This leads to persistent cell division. This persistent cell division seems to be related to telomeres. Telomerase, the enzyme needed to extend telomeres, is activated in 90% of tumors, resulting in longer cancer cells than other somatic cells.



[National Cancer Center: Cancer Cell Division]

2.1.3 Cancer Treatment

Cancer treatment generally includes active treatment (surgery and radiation, chemotherapy, immunotherapy) and palliative care. Among them, palliative care focuses on improving the quality of life of patients rather than treatment, and does not aim at cure. Radiation therapy and chemotherapy among active therapies are fields that try to increase survival rate with traditional treatment methods, but the side effects are large. In addition to cancer cells, the normal cells of the patient are destroyed, thereby reducing the basic immune function. Therefore, the emerging field is the field of immunotherapy / cell therapy, which has an effect on treatment with fewer side effects. Immune cell therapy is called as the fourth generation of cancer therapy and is in the spotlight as the next generation of cancer therapy.

2.1.3.1 Surgery

Surgery is divided into diagnostic surgery, radical surgery, preventive surgery and palliative surgery, depending on its purpose. Diagnostic surgery is used to confirm the cancer, and biopsies are included.
Radical surgery is a surgery that is useful for the early stages of cancer treatment and involves the removal of both lymph nodes and primary lesions surrounding the tumor.
Preventive surgery means surgery to remove the cause of cancer by removing polyps that can metastasize to cancer in advance.
Palliative surgery is a surgery aimed at reducing tumor size, delaying tumor growth, alleviating symptoms caused by cancer and improving the quality of life of patients.

2.1.4.2 Radiation Therapy

Radiation is often thought of as X-rays and in cancer treatment, it refers to means high-energy radiation. There are two types of radiation used for surgery: electric radiation (X-rays made of photons, ultraviolet rays, etc.) and particle radiation (neutrons, proton beams, etc.). Among them, gamma rays, electron rays, proton rays, and neutron rays are mainly used for cancer treatment.

Therapeutic mechanism directs radiation directly to the cell and directly or indirectly affects the DNA and cell membranes in the cell, causing the cell to die. Some of the cells that receive radiation die during cell division, and some of them age and undergo self-killing. This is because both normal cells and cancer cells work the same, so it is more effective to perform radiation therapy on characterized cancer cells and fewer normal cells. In the case of repeated treatment, normal cells have some recovery ability after a certain period of time, but in the case of cancer cells, it is impossible to recover enough, hence it is important to monitor this period to perform repeated treatment However, serious side effects have been reported that inhibit the proliferation of bone marrow cells.

Recently, due to the development of radiotherapy equipment, three-dimensional molding treatment is performed in 3D, and local treatment is very accurately performed using radiation generated by a high-tech linear accelerator. Image-guided radiation therapy also minimizes errors by adding imaging devices such as CT, MRI, and PET. Proton therapy, which treats patients with protons obtained by accelerating hydrogen atoms, is one of the newly introduced radiation therapy.

2.1.4.3 Chemotherapy

It is a method of treating cancer cells spread throughout the body by injecting anticancer drugs. This makes anti-cancer drugs that act differently depending on the cell cycle in which cells divide (the method that suppresses and kills part of the cell division cycle), and can be effective in cases where the patient is fit.

2.1.4.4 Immunotherapy

History of Cancer Immunotherapy

	1970s	1980s	1990s	2000s	2010s
Treatment	Immune booster	Cytokine therapy	Vaccine therapy	Immune checkpoint inhibitor	Immune checkpoint inhibitor
Summary	Overall increase of immunity. Effects are limited	Cytokine is a signaling substance that controls and stimulates the body's defense system. It is a protein active substance secreted mainly from white blood cells. Overall increase of immunity. Effects are limited	US FDA Approved for Prostate Cancer	Structure of cancer cell that brakes immune cell Great effect in some, who do not show improvements with other anticancer effects	Reported to be effective in treating leukemia

Efforts to use immunity to treat cancer have not been attempted in recent years but have been around since the 1970s. In the 1980s, immunotherapy with cytokines was used, and in the 2000s, there was a strong movement to use immunotherapy for more systematic treatment.

The most desirable chemotherapy is a **treatment that selectively kills cancer cells and does not damage normal cells as much as possible**. All of our usual chemo and radiation treatments damage normal tissues. Immunization is the treatment to remove cancer cells by using immune mechanism, which is one of the defense systems against diseases of the human body while minimizing these side effects.

Immunotherapy can be broadly divided into **active immunization**, in which an individual actively produces antibodies and sensitized lymphocytes, and **passive immunization**, which receives components of an immune response already made in the body of another person or animal.

Cell therapy also mentioned below can be thought of as part of immunotherapy because it is a therapy that uses cells that function in the immune function present in our body.

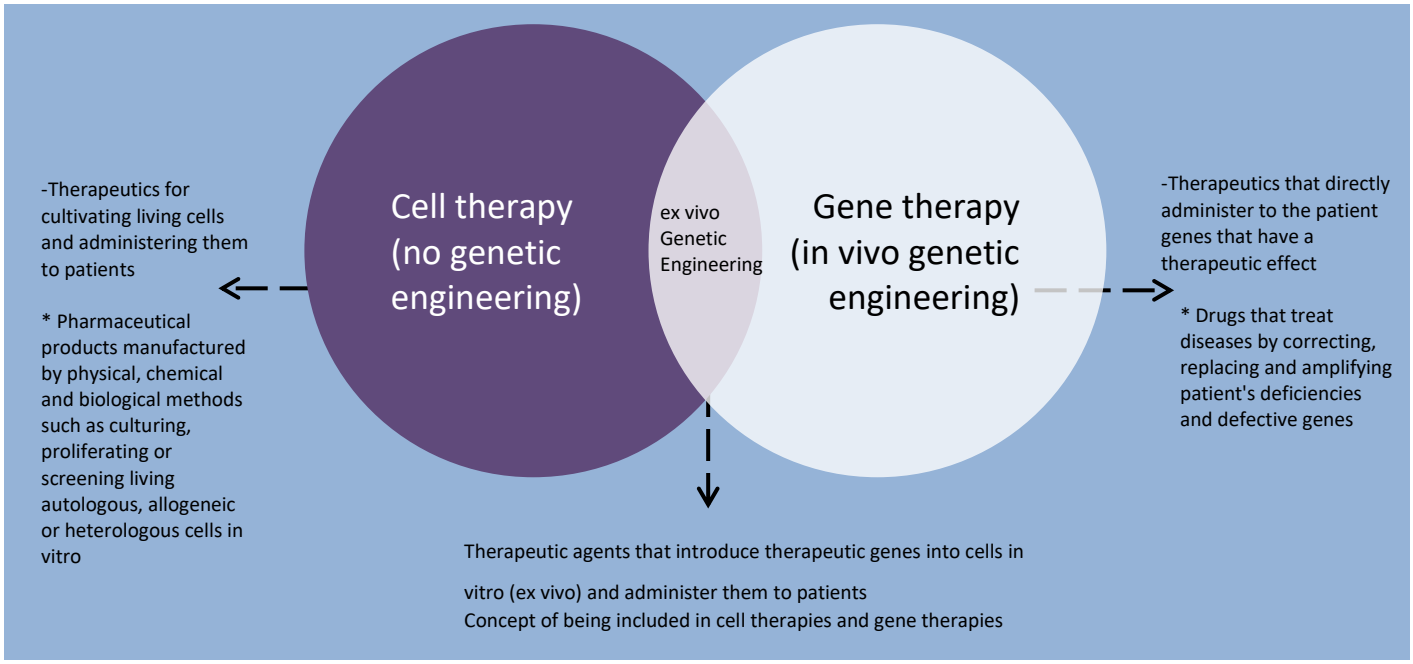
2.1.4.4 Cell Therapy

There are various definitions of cell therapy products. The basic idea is to "**inject living cells directly into the patient**." In more detail, it can be described as "**a drug manufactured by physical, chemical or biological methods such as culturing, propagating or selecting living autologous, allogeneic, or heterologous cells in vitro**." However, in the medical institution, the case of doctor performing autologous or allogeneic cells with minimal manipulation (simple separation, washing, freezing, thawing, etc. within the range of maintaining biological characteristics) without any safety problems during the operation or treatment is excluded.

* KFDA Notice: Regulations on Product Approval and Review of Biologicals

Fields	Details
Stem Cell Therapy	Biopharmaceuticals developed for the purpose of treatment of stem cells, which are cells capable of self-reproduction as repetitive division and differentiation into specific cells
Tissue Engineering	Medicines used to regenerate, repair, replace, or replace human tissue by culturing or proliferating cells or tissues derived from humans / animals or by combining them with cell secretions, biomaterials, and scaffolds, and making them into tissues
Immune Cell Therapy	Biopharmaceuticals that use immune cells, which function to remove infected cells and maintain immune system balance, to enhance their original function through in vitro culture, proliferation, differentiation, and genetic transduction
Somatic Cell Therapy	Medicines that use tissue cells, which have already been differentiated, and are used for tissue regeneration using cells isolated and cultured from skin, cartilage, cornea, pancreatic islets, and nerves.

(Scope) Cell therapy is divided into stem cell therapy, tissue engineering product, immune cell therapy, and somatic cell therapy

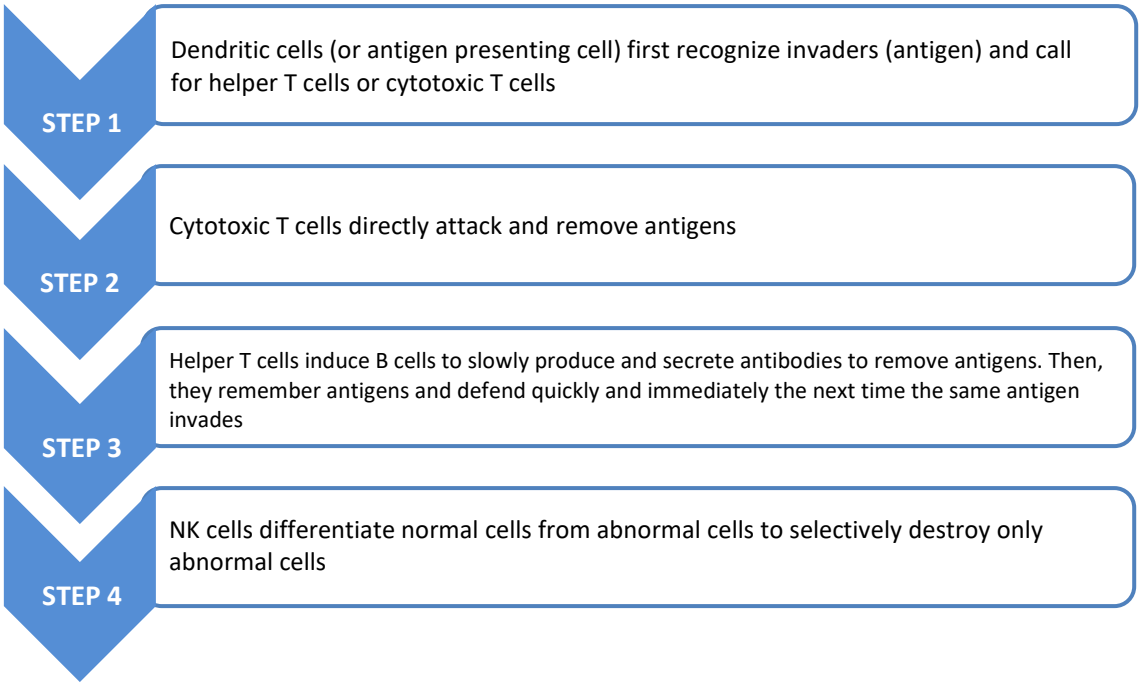


[Source: FDA guideline reference]

(1) Principles of Cell Therapy

In the blood, various blood cells are produced by differentiation from a kind of stem cells called hematopoietic stem cells. Representatively, leukocytes, red blood cells, and platelets are produced. Among them, **leukocytes** are divided into **myeloid lineages** such as eosinophils, neutrophils, basophils, and macrophages, and **lymphoid lineages** such as T cells, B cells, and natural killer (NK) cells as mentioned in Section 2.1.2. Cell therapy is basically a treatment performed by the immune system inherent in our body. It is divided into innate immune system and adaptive immune system to cope with harmful invaders (viruses) and internal harmful changes (cancers, etc.).

Among them, the **innate immune system** is already defined in the shape of cells, and when a universal saliva particle is detected, it reacts quickly and is eliminated. Leukocytes of the myeloid line are mainly involved here for treatment to occur.



[Cell Therapy Principles of the Adaptive Immune System]

The **adaptive immune system** is slowly progressing at first, but T cells or B cells with different receptor shapes are involved in response to various invaders. NK cells participate in both reactions and crosslink.

(2) Type of Cell Therapy

Classification by Cell Type

- **Stem cells:** Medicines that are manufactured using cells that do not differentiate into specific cells but have the ability to differentiate into cells such as nerves, blood, and cartilage, if necessary.

There are embryonic stem cells, adult stem cells, and degeneration differentiation stem cells.

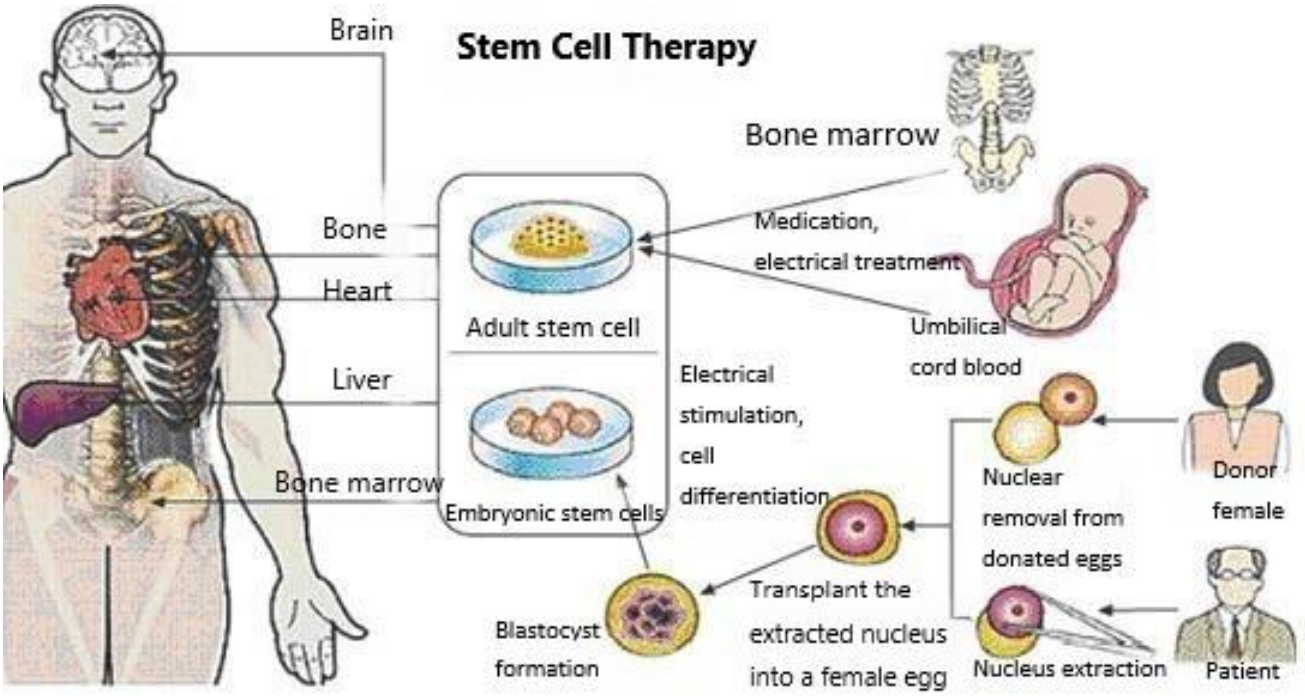
- **Somatic cells:** Medicines manufactured for the purpose of tissue regeneration using cells such as skin, cartilage, heart, and nerves

- **Immune cell:** Classification according to the origin of drug cells manufactured by using human immune cells such as dendritic cells, NK cells, lymphocytes

- **Autologous cells:** Cells collected from the patient's body, cultured and expanded in vitro or manufactured by physical / chemical / biological methods and administered to the patient.

- **Allogeneic cells:** A method of taking cells from another person's body and multiply them in the same way

- **Heterogeneous cell:** A method of taking cells from animals other than humans and proliferating them as above and administering them to patients



[Source: FDA]

	Type	Detailed Type Examples	Example of applied diseases
Stem cells	Embryonic Stem Cells	Hematopoietic stem cell Mesenchymal stem cells	Cardiovascular disease Spinal cord injury Arthritis, diabetes
	induced Pluripotent Stem cell (iPS')		
	Adult Stem Cells		
Immune cells	T Cells	Tumor Infiltrating T Cell CAR[5]-T Cell TCR[6]-T Cell	Leukemia, Lymphoma, Liver Cancer, Lung Cancer, Prostate Cancer, Autoimmune Disease
	NK cells	CAR-NK Cell	
	Dendritic cells	Genetically engineered dendritic cell	
Somatic cells	Epidermal cells	Epidermis, dermal cells	Skin burns, scars
	Chondrocytes	-	Degenerative arthritis

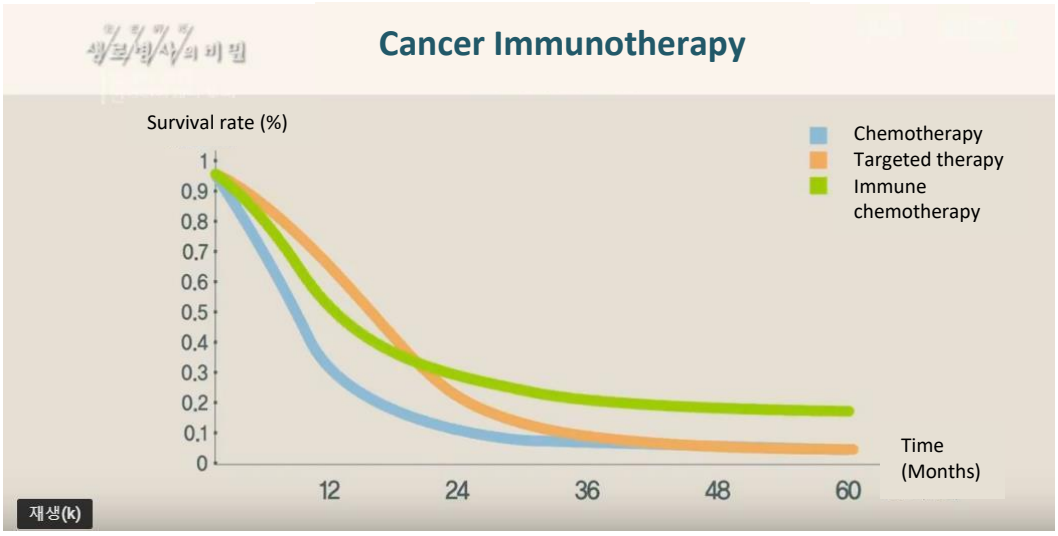
(3) Pros and Cons of Cell Therapy

One of the differences is that cell therapies are the ones that are closest to 'personalized' if the existing drugs were made due to the common characteristics of the disease. In addition, the use of autologous cells would be the method of treatment with the least side effects if the safety and culture safety in the post-cell harvesting process were secured. As a result, global biopharmaceutical companies aiming to develop new drugs are becoming new growth materials. However, there are limits to stem cell therapy, which is very popular.

Limitations of Stem Cell Therapy

- Stem cells, which can be transplanted into the human body and differentiate into multiple cells, seem to be enough to attract attention, but the disadvantages include high production costs and the cost of entering the clinical stage until approval, and guarantees after treatment.

- In addition, there are cases in which stem cells are not cultured in terms of safety, and this is equivalent to medicines when the stem cells are separated and multiplied, and medical procedures are used. The part used in the beauty field is the part that directly uses stem cells for medical procedures.



Another advantage is that immunotherapeutic drugs have a "memory" function even after the end of treatment, which is known to continuously work as an immune mechanism in the body. In other words, even after treatment, the mechanism of protecting the body lasts for a certain period of time.

(4) Overseas R & D Trend

LAK Cell

- Rosenberg of the National Cancer Institute (NCI) in 1987 reported about 30% treatment effectiveness using a Lymphokine-activated killer (LAK) to treat melanoma, renal cell carcinoma, and colorectal cancer
- LAK cells were difficult to mass-produce and had side effects due to a protein called IL-2 that was administered together to sustain anticancer effects.

CIK Cell

- Study on Cytokine Induced Killer Cell (CIK), a killer cell treated with cytokine, a physiological activator that promotes the activation of the immune system was conducted

- CIK cells are made by separating immune cells from their blood and then treating cytokines. They are powerful immune cells that selectively kill cancer cells by secreting interferon-gamma (IFN-r) and cancer necrosis factor (TNF-a)

- Confirmed the possibility of overcoming the limitations of existing anti-cancer therapies as a cancer prevention and cancer treatment

Provenge

- In 2010, Dendreon of the United States licensed Provenge, a dendritic cell therapy vaccine for prostate cancer
- This is the first developed country to be approved for immune cell therapy, which extends the lifespan of prostate patients by an average of 4 months
- Starting with this product, many researches and developments for anticancer immune cell therapy are underway around the world

Chimeric antigen receptor-T cell

- Cells that have genetically recombined cancer cell antigen-binding receptors and T cell activation signaling systems
- University of Pennsylvania's research team focuses on global attention by presenting a study showing 92% complete response rates in 39 children with acute lymphocytic leukemia (ALL)
- Since the publication of this study, 2nd and 3rd generation CART-T are being developed by reducing side effects of 1st generation CAR-T and changing target antigen

Company Name	Product Name	Usage and Efficacy	Approved Market
Avita Medical	ReCell	Skin disease	Sold in Europe, Canada, China and Australia
BioD	BioDfence	Adhesion prevention	Sold in the US
BioD	BioDfence	Wound treatment	Sold in the US
Educel d.o.o	UroArt	Bladder ureter reflux	Sold in the Slovenia
Fibrocell Science	Azfcel-T	Skin disease	US FDA Approved product
Genzyme, Sandi	Carticel, Carticel Plus	Joint damage	
Genzyme, Sandi	Epicel	Burns	
MacroCure	CureXcel	Wound treatment	Sold in Israel
Mmedx Group Inc	EpiFix	Wound treatment	US FDA Approved product
Organogenesis Inc	Dermagraft	Diabetic immediate ulcer	
Organogenesis Inc	Gintult	Periodontal disease	
Organogenesis Inc	Aplgraf	Diabetic immediate ulcer	
Orthofix	Trinity BJTE Trinity Evolution	Musculoskeletal damage	Globally Marketed and sold
Orthofix	Remestemecel-L	Graft versus host	US FDA Approved product
Osiris Therapeutics	Grafix	Wound treatment	
Osiris Therapeutics	Prochymal	Graft versus host	US manufactured, approved in Canada and New Zealand
TETEC Tissue Engineering Technologies	Novocart Inject Novocart 3D Novocart Disc	Joint damage	FDA clinical trials in progress, Marketed in Europe
TiGenix NV	Chordro Celect	Joint damage	FDA clinical trials Phase 3 completed, marketed in Europe
Anterogen	Cupistem	Crohn's disease	Korean FDA approved

[Source: Cell Therapeutics in Clinical Trials, May 2016, Frost & Sullivan, Hi Investment & Securities Co.]

So far, the field of cell therapy is concentrated in areas other than cancer, but the phenomenon of targeting cancer is increasing as shown below. Among them, the ratio of NK cells is also gradually increasing.

Company Name	Pipeline Name	Application in progress	Clinical stage	Remarks
Vigencell	VT-EBV-N	NK/T cell lymphoma	Clinical phase 2	Autologous
		Lymph proliferation disease after transplantation	Researcher clinical	Allogeneic
Eutilex	EBViNT	NK/T cell lymphoma	Clinical phase 2	Autologous
CelMedia	CM003	NK/T cell lymphoma	Clinical phase 2	Autologous
		B cell lymphoma, Hodgkin's Lymphoma, Lymph proliferation disease after transplantation	Clinical phase 2	Autologous
ATARA Therapeutics	ATA129	Lymph proliferation disease after transplantation	Clinical phase 3	Allogeneic / Third party
		EBV benign tumor	Clinical phase 2	Allogeneic / Third party
	ATA188	Multiple sclerosis	Clinical phase 1	Allogeneic

[Source: EBV Target by global companies, CTL Pipeline Comparison, Vigencell, Hi Investment & Securities Co. Research Center]

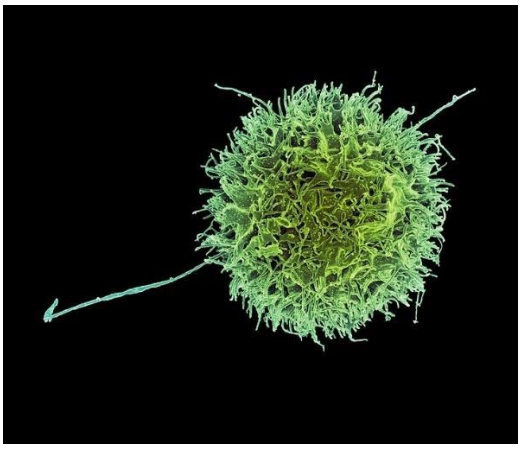
(5) Domestic R & D Trend

In 2001, Sewon Cellontech's arthritis treatment Chondron was first sold in Korea. 15 products, including Holoderm (A burn treatment based on self-derived skin keratinocytes. When severe second degree burns occupy more than 30% of the body surface area, it is implanted into the wound to create the epidermal layer), bone cell therapy, adipocyte therapy, and anticancer immune cell therapy, are licensed and 13 products are sold. About 80% of them are cartilage and skin regeneration treatments, and two anticancer immune cell therapies are Creagene's CreaVax-RCC Inj. (dendritic cells) and Ixel Cells (activated T lymphocytes) of Green Cross Cell. Cellular treatments are being actively conducted in Korea, and clinical research is increasing rapidly.

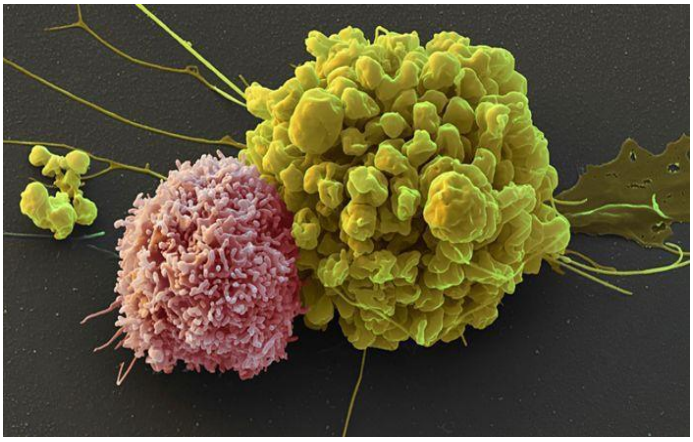
Classification	Product Name Code Name	Company	Development Stage	Application in Progress
Dendritic cells	Creavax-HCC	JW Creagene	Clinical phase 3	Liver Cancer
NK Cell	CB-IC-01	Cha Biotech	Clinical phase 1	Ovarian Cancer
	MG4101	GC Labcell	Clinical phase 1	Ovarian Cancer

[Anticancer immunotherapy in clinical trials, May 2016]

2.2 What Is NK Cell (Natural Killer Cell)?



[Colored Scanning Electron Micrographs of NK Cells Credit: NIAID]



[Natural Killer Cell (NK cell: Pink): Attacking yellow Tumor Cell; Credit: Eye of Science/SPL]

Since NK cells were first reported in a paper in 1975, active research has been conducted as an important research cell. Recently, NK cells have been confirmed to be capable of removing cancer cells and have been used in cancer treatment clinical researches worldwide. However, the problem is that the number of NK cells, one of these important immune cells is only about **10% of the body's immune cells**, and there is a disadvantage that the culture is not good even if the cell culture. Though, it has been found that NK cells, among other various immune cells, are **effective in directly preventing the development, proliferation, metastasis and recurrence of cancer**.

In addition, cancer causes the body to lose important cells that treat cancer because anticancer drugs destroy these NK cells. Therefore, cancer treatment using NK cells uses a method of taking out NK cells in blood, incubating / proliferating, and then putting them back into the patient's body.

NK cells are immune cells that directly destroy virus-infected cells or cancer cells. They are a type of white blood cell. These NK cells are responsible for innate immunity. There are about 100 million NK cells in normal adult bodies, and unlike T cells, they mature in the **liver or bone marrow**. It is known to attack virus infected cells or tumor cells. The method first detects abnormal cells, and then perforin is sprayed on the cell membrane to melt the cell membrane to puncture the cell membrane. The granzyme is sprayed into the cell membrane to break down the cytoplasm, causing apoptosis, or by injecting water and salt into the cell to cause necrosis.

Cancer cell death is largely divided into two stages: cancer cell **recognition** and **attack**.

2.2.1 Cancer Cell Recognition

In order for immune cells to attack cancer cells, the first step is to know if they are foes. In other words, immune cells should recognize cancer cells as enemies.

Cancer cells were originally cells that are part of my body like normal cells, so even if NK cells have the ability to detect abnormal cells, it is not easy to find cancer cells. Originally, the cells of our body have receptor proteins that prove to be "self" on the cell surface, which is like having an ID that is unique to my body. This protein is called 'MHC', and in fact, many cancer cells also hide MHC. Fortunately, NK cells have receptors to detect defective MHCs in cancer cells, and NK cells have '**activation receptors**' and '**inhibitory receptors**' on the cell surface, which can **detect modified receptor proteins**.

NK cells, unlike T cells and B cells, which have antigen-specific receptors, express various innate immune receptors on the cell surface and can distinguish normal cells from cancer cells. NK cells recognize target cells (such as cancer cells) through various **activation receptors** or **inhibitory receptors** on the **cell surface**, and regulate their activity by a comprehensive signaling system induced therein.

2.2.1.1 Activation Receptor

NK cells recognize ligands that are expressed **when the target cell is in an abnormal state**, and there are intracellular molecules that increase expression **when the DNA of the target cell is damaged or when cancer occurs, or when infected** (UL16 binding proteins (ULBPs) and MICA/B,NKp46, NKp44, NKp30, 2B4, DNAM-1 activation receptors). These substances play an important role in detecting and eliminating cancer.

2.2.1.2 Inhibitory Receptor

The presence or absence of intracellular molecules expressed on the surface of target cells is mainly recognized. Typically, it expresses an inhibitory receptor specific for MHC Class I. **If the target cell lacks MHC Class I, NK cells will attack this target cell**. However, when MHC Class I of many target cells is high, its expression is reduced by stress such as cancer development or infection.

More easily expressed, there are many MHC Class I on the surface of normal cells, so NK cells do not attack. When cancer occurs, MHC Class I decreases and NK cells become "missing self" and attack.

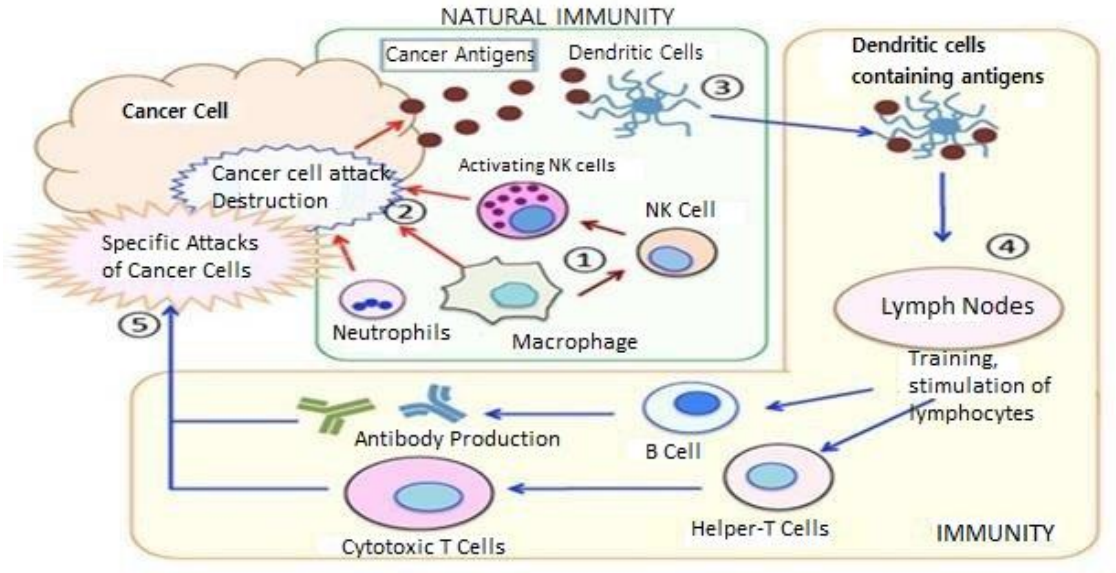
> NK cells usually play a role similar to killer T cells, but differ from killer T cells. Killer T cells are identified only by MHC Class I, the same concept as cell identity, and kill only when MHC Class I is not self (missing self) due to the virus. Natural killer cells also kill when MHC Class I decreases or disappears. Cancer cells may use these tricks to pass killer T cell checks.

2.2.2 Cancer Cell Attack

NK cells are important cells responsible for innate immunity and are known to attack virus infected cells or tumor cells. The method first detects abnormal cells, and then perforin is sprayed on the cell membrane to melt the cell membrane to puncture the cell membrane. Granzyme is sprayed into the cell membrane to dissolve the cytoplasm or inject water and salt into the cell to cause cell necrosis. When cancer cells are recognized, they may attack directly, but they may indirectly attack by activating cytokines and activating cytotoxic T cells and B cells.

2.2.3 Cancer Cell Destruction Mechanism of NK Cell

The overall mechanism of cancer cell destruction including NK cells is as follows.



1. Activated macrophages activate NK cells.
2. When activated macrophages and NK cells attack cancer cells and destroy them, cancer antigens are absorbed by dendritic cells.
3. The primary defense against cancer cells that do not require sensitization by antigen becomes "natural immunity".
4. Dendritic cells phagocytosis of cancer antigens are activated by transmitting information of cancer antigens to T cells and B cells.
5. Cancer antigens Attacks of cancer cells by specific immune responses become "acquired immune".

2.2.4 Advantages of NK Cells in Chemoimmunotherapy

NK cell therapy is attracting attention as a next-generation therapeutic that can **be combined with the three major cancer treatments** of surgery, chemotherapy and radiation therapy, along with basic functions (the ability to find and kill cancer and activate other immune cells). NK cell immunotherapy has the advantages of preventing and treating cancer, disease, delaying resistance to anticancer drugs, synergy with radiation, chemotherapy and combination therapy, reducing pain, no side effects, and improving the quality of life of patients.

In addition, cancer stem cells may metastasize and relapse several years after the cancer has been cured clinically. Cancer stem cells play an important role here. Because these cancer stem cells have strong resistance to anticancer drugs and radiation treatments, they are likely to remain somewhere even if the cancer is considered clinically eliminated. Because the cancer stem cells in the latent state proliferates and differentiates again, cancer recurs again. Therefore, cancer stem cells should be removed to prevent cancer from recurring and increase the likelihood of effectively curing cancer. That method can be achieved through NK cell therapy. In other words, NK cells have the **function of finding and killing cancer stem cells**.

2.2.5 NKT Cell (Natural Killer T cell)

There is another cell that finds and removes cancer cells like NK cells, which is **NKT cell** that has the **characteristics of NK cells and T cells**. These NKT cells perform immunomodulatory and immune enhancing activities in various immune diseases. As NKT cells become more active (when NKT cells are activated), they **release various cytokines in a very short time**, and **secreted cytokines activate dendritic cells, NK cells, T cells, macrophages, and B cells to increases and suppresses immune response** (effector cells, such as NK cells and killer T cells, may also promote cancer cell attack).

Overall, NK cells and NKT cells are so similar that they both have NK cell receptors and have a larger size in common than other T cells. The difference is that NKT cells mature in the thymus, NK cells mature in the liver or bone marrow. NKT cells are a type of T cells that express rearranged T cell receptors (TCRs), or T cell receptors, but NK cells lack this TCR. In addition, NKT cells are smaller in size than NK cells (NK cells are classified as large lymphocytes and are the largest among lymphocytes), and when an enemy is recognized, **they can attack directly or indirectly** by activating cytokines to activate cytotoxic T cells and B cells.

NKT cells **secrete** a large amount of cytokine, an immune cell activator, **interferon gamma (IFN-γ)**. **NKT cells can play the role of NK cells to kill cancer cells without MHC and to kill cancer cells with MHC at the same time. NKT cells are the most feared immune cells for cancer cells, but there are only 0.1-0.3% in the blood and fewer in cancer patients.**

By releasing interferon gamma, a network of immune cells is activated, as well as various immune cells in the body that attack cancer cells, such as various T cells (helper T cells, killer T cells, gamma delta T cells), NK cells, dendritic cells, etc. simultaneously. While **activating**, it has been found to acquire the long-term **cancer attack memory** of immune cells.

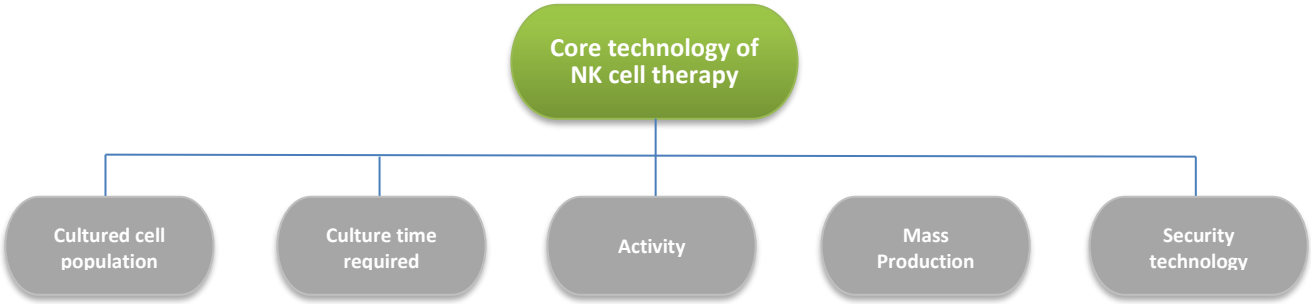
NKT is present in organs such as the thymus, liver and bone marrow, and in small amounts in the spleen, lymph nodes and blood.

In a domestic study, activating NKT cells in the body of a cancer-causing mouse increased cytotoxic activity and increased IL-12 secretion through dendritic cells, which inhibited cancer metastasis and growth. Activation of NKT cells has also shown that NK cells are activated and influence the removal of cancer cells.

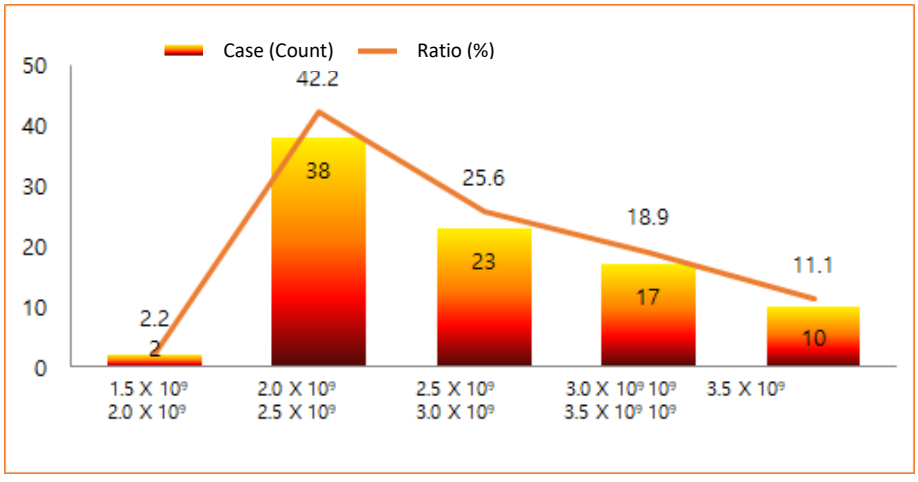
2.2.6 Excellence of NK Cell Culture Technology

2.2.6.1 Core Technology of NK Cell Therapy

Although NK cell therapy is a common part of mass production technology and stability technology like other cell therapy products, the uniqueness of NK cell therapy are the number of cultured cells (how many have been cultured) and the time required for culture (how long it took to be cultured), and NK cell activity (how active the cultured NK cells are).

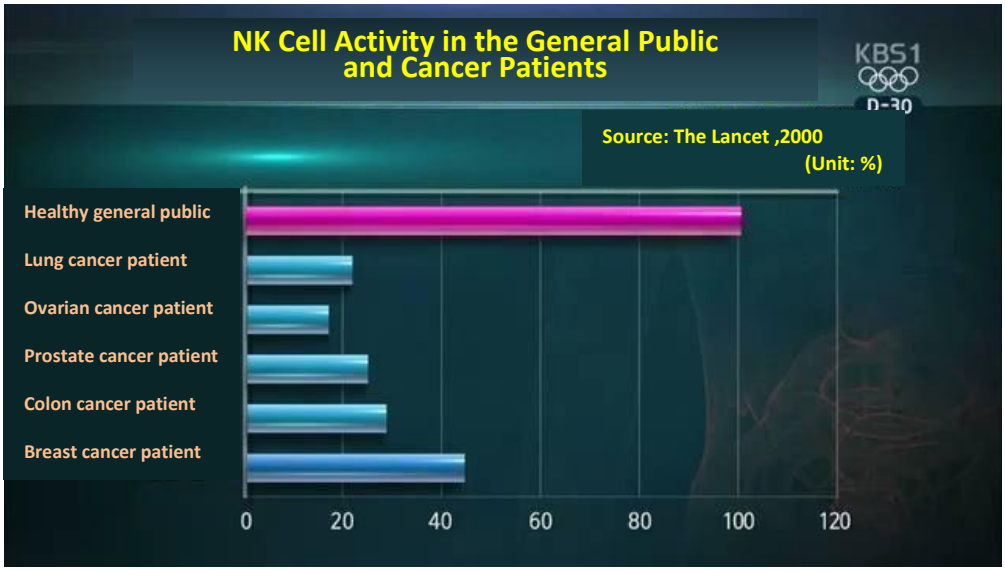


The following shows the number of NK cells and the ratio of NK / NKT cultured in the actual experiment.



[NK cell quantity]

The figure below shows the difference in NK cell activity between normal and cancer patients. As can be seen in the picture, cancer patients show low activity.



"NK cell activity" is a term that expresses the state in which the NK cells are activated and expresses cytotoxicity effectively in the body. **If the activity is low** even in the case of NK cell population being appropriate, **the immune function is not properly expressed, causing disease**. The activity of cultured NK cells activates other immune cells to effectively kill pathogens (cancer cells, other disease cells, etc.) or indirectly attack when cultured NK cells are injected into the patient group.

Safe
There is no side effect and is stable when administering because it does not use cancer cells used as genetically engineered or support cells

High IFN-gamma
High levels of IFN-gamma, a natural killer indicator, are expressed in cultured cells

Excellent cancer cell killing ability
Cancer cell killing ability is excellent due to expression of a number of representative activation receptors such as NKG20, NCRs, and DNAM-1

Patient customized
There is no limit to the target, and the cell ratio can be adjusted according to the patient's disease

Stable
Stable yield due to standardized manufacturing process

Effective against solid cancer
Highly expressed DNAM-1 activating receptor that is not affected by tumor microenvironment is effective for solid cancer

Total cell count
Total cell count is at least 4 * 10^3

Significantly higher yields
NK cell rate can be obtained up to 98.5% compared to other companies

[Safety and Stability of NK Cell Culture]

- Cultivation and research of other immune-related cells other than NK cells are being conducted, but NK cell culture field possesses technological excellence of Korean bio companies
- Excellent ability to treat cancer of autologous NK cells and few side effects
- When developing autologous NK cell therapy, treatment cost is significantly lower than other immune cell therapy
- NK cell culture development
- Highest level of NK cell culture environment composition technology
- High purity, high activity, shortest time, and ultra-high-volume NK cell culture
- Korea's best technology in NK cell culture and activation
- NK cell shortest time most culture capacity
- Signed technology transfer contract and co-clinical promotion contract with overseas authorized national medical institutions related to NK cells for the first time in Korea (National Cancer Center, Mongolia)
- Signed an MOU with Chung-Ang University for joint clinical promotion and overseas technology transfer business for the clinical promotion of autologous NK cell therapy
- Joint research is underway by applying to the “International Tuberculosis Research Institute” under the Korean Tuberculosis Center for research on the killing of super tuberculosis bacteria through NK cells
- NK Cell's first-generation company, KOSDAQ-listed company NKBio's core research personnel
- Upgraded technology of NK cell treatment that was not completed due to bankruptcy of NKBio
- Core technology of NK cell culture is culture medium. KBG realizes the highest level of NK cell culture capacity through its own culture solution manufacturing technology.

[Research achievements and history]

2.3 Technology Competitiveness of NKCL

2.3.1 High NK Cell Yield

The key to commercializing NK cell therapy is the technology of culturing cells in large quantities. NK cells are difficult to culture compared to other immune cells such as T cells, and in order to remove cancer cells and disease-causing cells generated in the human body, a greater amount of NK cells should be added.

NKCL has dramatically increased the number of NK cell cultures through specialized culture environment manufacturing technology and cultivation source technology optimized for NK cell culture. Each culture has its own optimal culture for cell culture. NKCL constructed 12 optimal culture environment recipe

databases by combining various environments necessary for cultivation such as temperature, humidity, culture components, and enzyme concentration. Compared with the existing method capable of culturing 200 to 400 million cells, the average number of NK cell culture of 2 to 4 billion cells was achieved.

2.3.2 Targeted Treatment

It is targeted therapy that raises the efficiency of NK cells to the maximum. In general, when NK cells are administered for cancer treatment, only a small amount of NK cells attack the cancer, and other NK cells exert a dispersing effect on other non-lethal diseases. However, NKCL has dramatically increased the percentage of NK cells that attack specific cancers through targeted therapy, and focuses on the five most common cancers (lung cancer, liver cancer, stomach cancer, colon cancer, and breast cancer), and conducted research on five major cancer treatments in progress.

2.3.3 Automated Culture System

Existing NK cell cultures were very low in productivity because they depended on the entire research process of professional researchers. NKCL is pursuing the development of an automated system that can automate NK cell culture by introducing artificial intelligence (AI) that finds a culture environment optimized for NK cell culture.

By controlling the cell culture process with artificial intelligence, it is possible to reduce the dependence on experts, prevent human errors in advance, improve the overall quality of production, and block the outflow of technology through human resources.

Above all, the introduction of an automated system can improve production efficiency by more than 100 times, reducing production costs and lowering the price of treatment, contributing to the mass production and popularization of NK cell therapy.

2.3.4 Automation and AI in NK Cell Culture

As with all medicines, the biggest drawback of NK cell therapy is also the selling price. More precisely, the cost of the facility to cultivate and the cost of cultivation to the actual cultivation would not be possible without mass production. There is a need for a technique for culturing in large quantities while maintaining the quality of cell culture. Making the quality itself high is supported by experience and R & D through several trials and errors, but when it goes to mass production, the know-how made by human power is limited, and the machine can take care of the situation related to culture on its own. It is necessary to have an environment where it can be judged automatically and cultivated in a better direction, sometimes like a human with know-how.

It is not a problem to be solved if only the cultivation device is automatically cultured in a GMP facility. The ultimate goal is to make various situations related to cultivation go through the machine learning stage and to use the deep learning AI to do the best things that researchers with know-how can do.

To this end, it is necessary to accumulate various know-hows related to continuous data collection, classification, and cultivation, and to create optimal conditions for cultivation by combining high-tech IT technology.

It is true that when we hear AI, we think it is something difficult. When the 4th Industrial Revolution comes to mind, along with blockchain, big data and AI continue to enter the realm. The reason is that the direction of the developing society is a more advanced and developed, so it is hard to achieve it for the purpose only by human power, so we try to achieve the desire of the machine.

The same applies to the medical field. Big data and AI are emerging fields when investing in new drugs. The same holds true for manufacturing technology, and in many areas we don't know, AI is truly taking the next step in the new world.

The same is true for NK cell culture as well. The know-how cultivated by skilled researchers can be transferred to the machine and lead the culture in a better direction. This will allow mass production, but can also increase the quality of the culture itself. It's too difficult and time-consuming and expensive to do every single case that humans can think of under the same conditions. However, we believe that the introduction of AI can reduce these trials and errors and produce the desired results in a short time, resulting in the most ideal result of personalized NK cell culture.

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BLOCKCHAIN INTRODUCTION BACKGROUND

1. Introduction Background

1.1 Preface

Personal Data & Personal Health Record

There are many different types of data associated with individuals who exist on the Internet or offline. Data is distributed in an unsecured form or in a secured form, although the distribution of data is by transaction or simply in the form of transmission.

The important thing is how these data move and how they are managed. For example, where and how the data that is relevant to me is managed is very important.

At the moment, it is poorly managed and technically vulnerable to security. Moreover, when the data being handled contains sensitive personal information, it can be more than just storage and security.

The data covered by the NKCL project contains these sensitive areas. As the business expands, the preservation and management of data will become a very serious problem. Therefore, we would like to solve this by combining with blockchain technology.

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BLOCKCHAIN UTILIZATION IN BIO INDUSTRY

2. Blockchain Utilization in Bio Industry

2.1 Global example

IBM is one of the leading companies applying blockchain to the bio industry.

IBM's Watson Health division worked with the US FDA on how to securely share patient data through blockchain technology. In addition, the company is seeking to implement accurate medical data by processing electronic medical records, clinical records, genomic data, and data extracted through various IT devices. IBM has made the data exchange transparent so that all transactions can be tracked using blockchain technology.

Another company is Encrypgen, which can create a blockchain-based genomic data marketplace where you can sell your genetic data for research without revealing the seller's personal information. As a platform, it provides a blockchain platform that connects individual DNA information to customers such as doctors, researchers and pharmaceutical companies. The purchaser purchases the Encrypgen ERC20 token and then purchases this DNA information with the seller's permission and returns the payout to the seller.

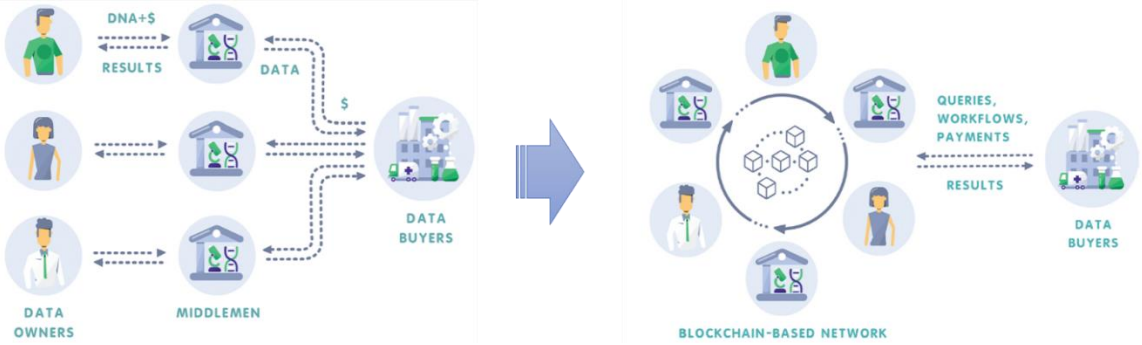

FIG 2.1 Before and after applying blockchain in DNA data trade

In addition, the Nebula model (Nebula Genomics: A startup co-founded by Harvard geneticist Dr. George Church), which can trade genetic information through direct linkage between owners and information consumers, using the decentralized nature of blockchain without a central manager, is being studied. The company's motto is, "If you give more control over your medical records, many health benefits will go directly to them." This is a testament to your lack of control over your data.

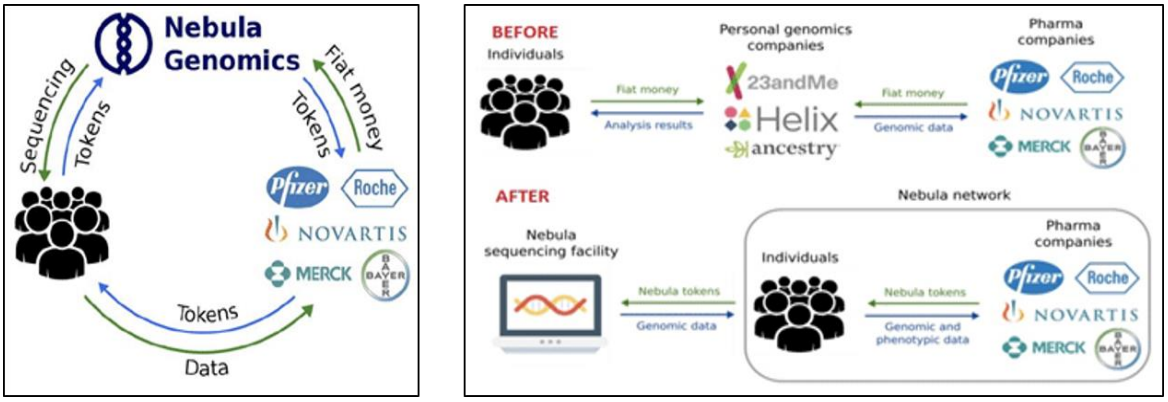

FIG 2.2 Nebula Genomic Blockchain

In Korea, many medical institutions store individual medical information separately. In the face of integrating personal medical information and addressing security issues, in 2017, MEDIBLOC launched the first blockchain that stores and manages the patient's medical information using the blockchain.

2.2 Necessity of Blockchain

If blockchain technology is introduced in the bio industry, it can be very useful for efficiently managing and storing human DNA and personal medical data. In the provision of personal medical information, data can be delivered while maintaining the protection of sensitive personal information.
Blockchain technology is highly utilized as a subject that delivers data while maintaining security of such data. However, the best that can be done at present is to be a private blockchain, a permissioned blockchain that can control information by authority and maintain confidentiality, not a public blockchain environment.
On the contrary, the introduction of blockchain can be an advantage because of the lack of centralized and systemic medical systems.
As blockchain is still being introduced to the financial and logistics sectors first, it is time to find ways to reduce the trial and error and apply blockchain technology efficiently to the medical and bio industries.

2.3 Personal Information and Blockchain

Blockchain has the property that internal data cannot be changed or destroyed. Therefore, legal review of the storage, modification and disposal of medical data is required under the Medical Law, and the way to implement it on the blockchain should be sought.
Also, consideration of 'Right to Data Portability' for requesting the data subject to send or transmit information to another data processor for the data processor that collects, processes or stores the personal information with the consent or contract of the data subject is needed.
This is specified by the European Union in the GDPR (General Data Protection Regulation) to strengthen the control of personal information on the data subject and to ensure more choice.

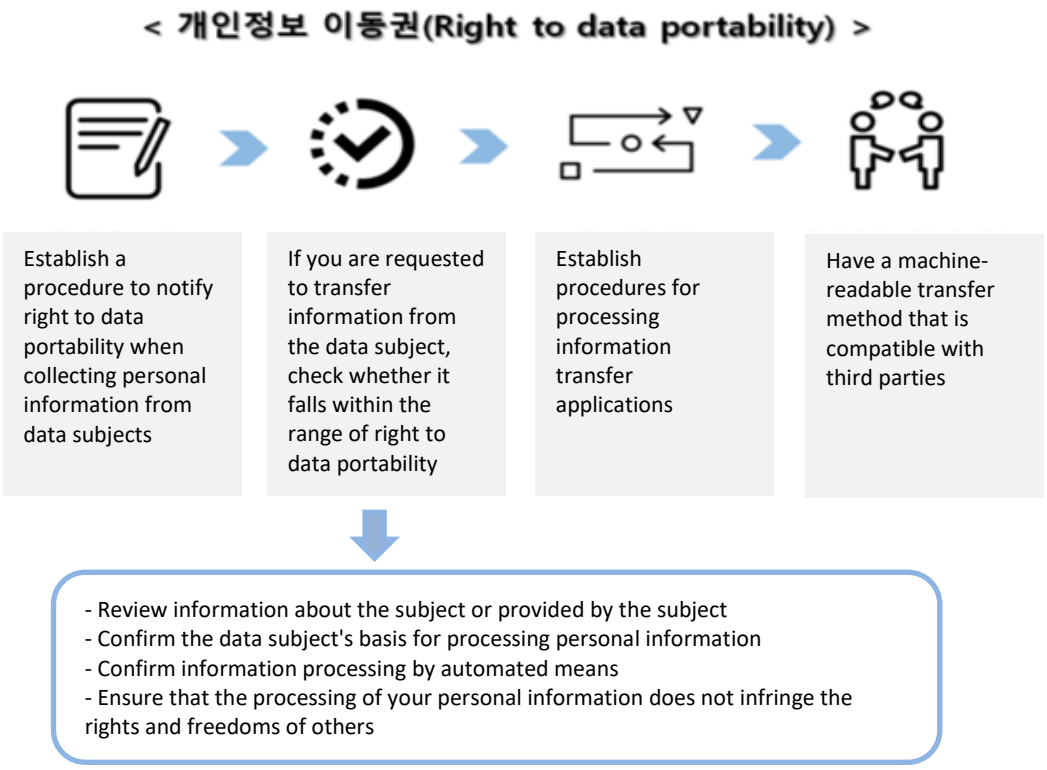

FIG 2.3 Right to data portability (Source: Ministry of Public Administration and Security, Korea Internet & Security Agency, GDPR primary guidelines for Korean companies)
Writing all data on the public blockchain makes it possible to protect the data from malicious hacking and prevent tampering. However, personal data privacy and alteration and deletion are impossible, which leads to problems that are opposed to 'Right to Erasure' and 'Right to be Forgotten'.

This can be solved by recording data on a private chain that is separated from the public chain through a double chain to control the access rights of the data, thereby making it possible to change and delete the data by the data subject while enhancing the security of personal data. Public blockchain is operated on-chain and private blockchain is separated and operated off-chain.

*** GDPR Article 17**
"The data subject can exercise the right to delete his personal information to the data processor, and the data processor will be obliged to delete the personal information without delay if certain requirements are met." In this case, a surcharge of up to 4% per year is added.

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UNDERSTANDING OF NKCL BIO-BLOCKCHAIN

3. Understanding NKCL Bio-Blockchain

3.1 Definition of NKCL Bio-Blockchain

3.1.1 What Is NKCL Bio-Blockchain?

NKCL Bio-Blockchain is a system that aims to build a "**trust platform for secure data management and ecosystem creation** based on blockchain."
The NKCL project basically begins with NK cell culture. In addition to the request for cell culture, the cultivation process, and the result, information on the health status of the user is data that helps in the development of technology, and comprehensive data indicating the individual's purchasing history and propensity are also data to be protected. Furthermore, the areas we deal with are closely related to the bioindustry, so data management created and distributed in these areas is also very important. This raises the question of how to secure this basic information and who manages it. The answer to this question is found in the blockchain and another design is needed because a simple public blockchain does not solve this problem. Therefore, in this project, to take advantage of public blockchain and private blockchain, we took a double chain structure, and in the existing double chain structure, the bridge role simply applies the consensus algorithm between chains. In this project, the difference is that a module is designed to play a clear role in cross-linking. Therefore, the Ethereum platform is used for the on-chain solution (1st Blockchain) and the Hyperledger platform is used for the off-chain solution (2nd Blockchain).

3.1.2 Composition of NKCL Bio-Blockchain

NKCL Bio-Blockchain is composed of 3 modules of NKCL Bio-NET based on Hyperledger and NKCL Bio-Blockchain Smart Gateway, which is linked with Ethereum mainnet to bridge data transmission.

3.1.3 Role of Ethereum Mainnet

The Ethereum mainnet lists the NKCL tokens on the Exchange and provides the foundation for trading. In other words, it provides a foundation for creating a universal token ecosystem. It is intended to facilitate transactions through tokens of the ERC-20 Standard. In the case of ERC-20 tokens, it is easy to manage as an asset because it is easy to trade through the Ethereum wallet or exchange and has high money exchange rate. In addition, it is characterized by the smooth creation of an ecosystem, including the expansion of the use of tokens through DApps.

3.1.4 NKCL Bio-Blockchain Smart Gateway

Medical information systems require high reliability, security and transparency. Blockchain technology has the characteristics to meet these requirements. However, the original blockchain technology may not be suitable for storing sensitive medical information because it is a technology that increases reliability through the propagation of information. Therefore, in order to overcome such limitations, the blockchain was formed by dividing the information that needs to be disclosed and the information that requires security by constructing it with a double chain.

This separation also requires both blockchains to require standards or interfaces to exchange information. Therefore, NKCL Bio-Blockchain Smart Gateway was developed as a smart gateway. The smart gateway is designed to have an independent role for the creation of the ecosystem in addition to the purpose of the interface between the two blockchains.
The NKCL Bio-Blockchain Smart Gateway serves as an intelligent interface for data exchange between both blockchain platforms and is used for the processing and monitoring of smart contracts (CAs), and for the exchange and management of data. In addition, it also has the function to create an ecosystem through interworking with NKCL DAPP, interworking with external Exchange, interworking with external chain, etc. (including NKCL Bio-API).

3.1.5 NKCL Bio-NET

As mentioned above, blockchain technology with scalability, that is, sidechain or off-chain technology, which is a layer 2 technology, is not suitable for commercial service in the development stage. At this time, the Hyperledger platform suitable for commercial service development is used to develop NKCL Bio-NET that satisfies scalability and security.
Hyperledger is recognized as a platform that can enhance access control and security by allowing access only to authorized nodes. Hyperledger is also useful for implementing transaction acceleration systems, distributed storage technology, distributed ledger technology, and certified authentication technology.
Kakao Pay has also switched to using Hyperledger technology for Kakao Pay certification in 2018.

3.1.6 NKCL DAPP and NKCL Bio-API Server

NKCL DAPP for the creation of bio blockchain ecosystem uses various information data through NKCL Bio-Blockchain Smart Gateway through NKCL Bio-API interface. Blockchain services such as payment, authentication, asset and account information search are provided through NKCL Bio-API server.

3.2 NKCL Bio-Blockchain Features

3.2.1 Double-chain Configuration for Security and Scalability

As the number of blockchain nodes increases and security increases, scalability decreases because transaction processing efficiency decreases. Consideration should also be given to maintaining the transparency of transactions and to protecting the information stored.
In order to meet the requirements of security and scalability to the maximum, NKCL bio blockchain uses Double-Chain, but maintains transparency, and utilizes Ethereum mainnet with general purpose in Layer 1 (On Chain). It is designed to leverage the Hyperledger platform for layer 2 (offchain) with a licensed blockchain that requires.

3.2.2 Smart Gateway for Heterogeneous Blockchain Interworking

The Ethereum mainnet and the Hyperledger platform have different data formats and therefore are not interoperable. To solve this problem, NKCL Bio-Blockchain Smart Gateway is placed in the middle to enable data exchange.
There is Tendermint's Cosmos project for heterogeneous blockchain integration, but it is

difficult to accept because it is not yet commercialized and is developed for various blockchain integrations.
The NKCL Bio-Blockchain Smart Gateway can shorten the development period because Ethereum's contract processing and Hyperledger and interworking are the primary goals. In addition, NKCL Bio-Blockchain Smart Gateway also provides NKCL token processing and token swap through token exchanger. It also has a policy manager for issuing and managing tokens, a CA controller, an interface manager, and a transaction manager to automatically handle contracts, and an NKCL API Server external module for interworking with multiple DAPPs.

3.2.3 Reward Plan for Participants

NKCL Bio-Blockchain actively accepts reward policy (reward plan) for participants to spread ecosystem.

The NKCL project basically cultivates NK cells, provides the results (FACS), and enables safe and transparent management of the culture and subsequent processes. In addition, providing users with their own records (such as personal health data before and after cultivation) makes it very easy to track the effects, and also helps to direct further culture. Gathering these data can benefit self and others as well. However, the limitation is that the provision of such data is owned and cannot be used without permission. In addition, such data is difficult to obtain unless you provide it actively. Therefore, if the reward is not followed, the motivation for providing the data will not easily occur. The reward plan for the participants is therefore very important in terms of data provision.

In addition, not only from the data but also from the token economy point of view, if the reward plan of the participant is not given, the degree or speed of activation is slow. This section may be referred to the token economy section.

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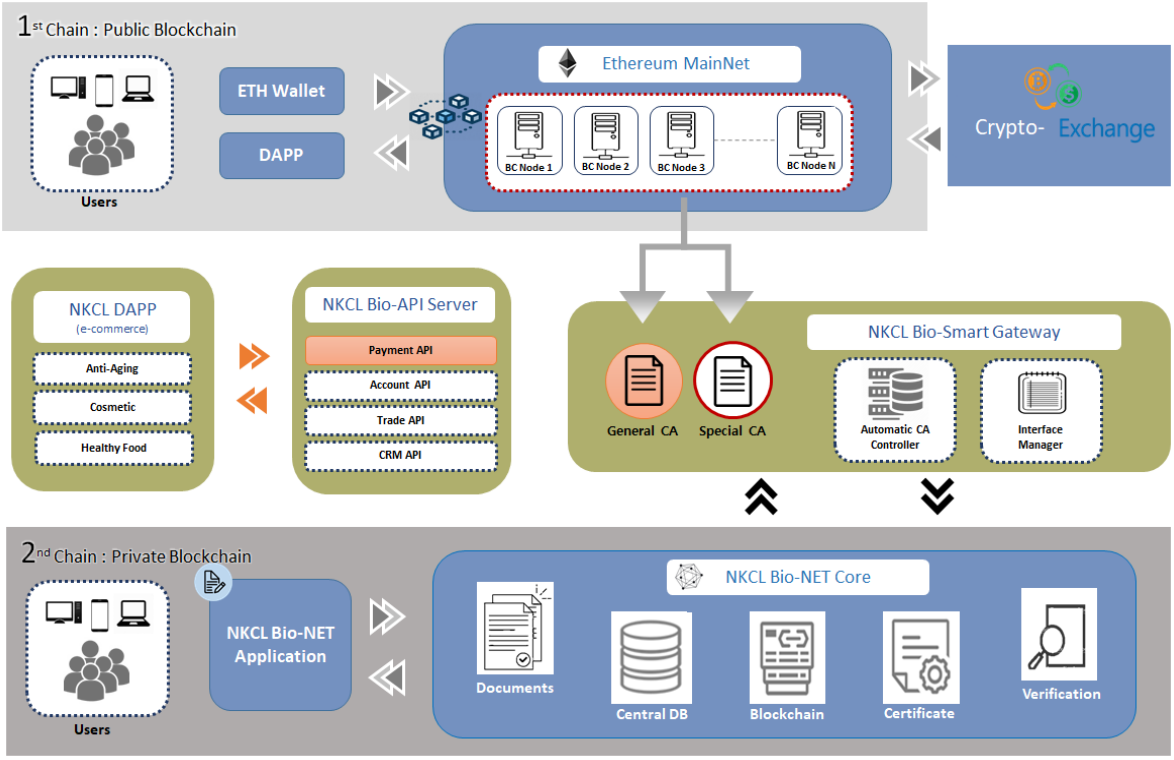
BIO-BLOCKCHAIN

4. NKCL Bio-Blockchain

4.1 Architecture

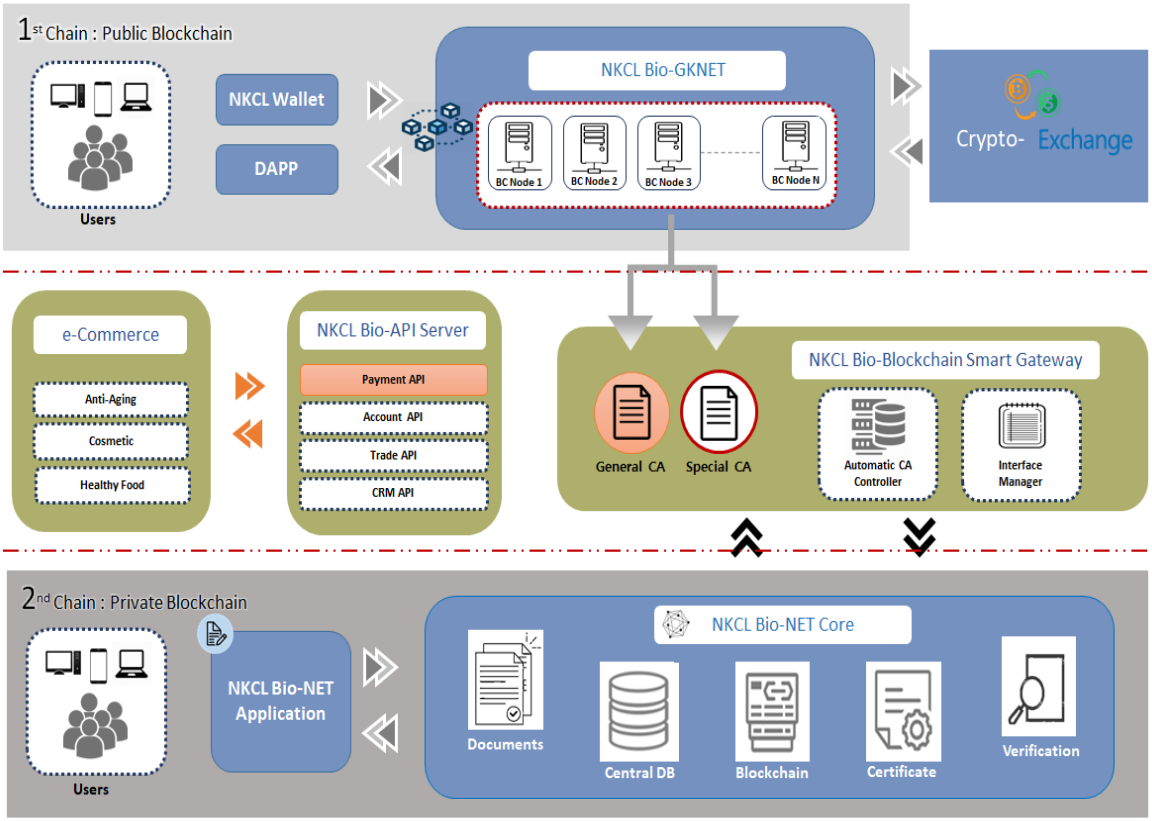
NKCL Bio-Blockchain has to list and distribute basic token (NKCL Token) on Exchange and deal with various information included in cell culture and business activities to maintain diverse ecosystem. Therefore, it is basically a dual-chain structure with two blockchains. In particular, if it is necessary to store sensitive information, including personal information, the relevant information will be handled securely using NKCL Bio-NET's Private Blockchain. In addition, the NKCL Bio-Smart Gateway, which acts as a bridge to combine these two blockchains, will act as a bridge between the public blockchain and the private blockchain. Smart Gateway increases security by connecting to NKCL Bio-API Server of Smart Gateway without directly connecting to NKCL Bio-NET even in the part that needs to be linked externally like a shopping mall.



[FIG 4.1 NKCL Bio-Blockchain Architecture]

Under the basic architecture described above, users will use tokens as a way of utilizing tokens on the public blockchain and NKCL brand tokens described later. Before the size of a transaction grows, the architecture described above is sufficient, but when NKCL token becomes popular, its own transaction speed moves on the Ethereum mainnet, so the speed is determined not only by the amount of NKCL token transactions but also by the total amount of transactions. As the Ethereum Foundation expects, it will be better if the proof-of-work changes in the next few years and the various technologies such as the sharding technology improve and the transaction speed improves. If not, the NKCL Bio-Blockchain may have to move its public blockchain into its own network. In such a case, as shown below, the mainnet should be considered separately so that only the first blockchain, the Ethereum blockchain, can be replaced.

In the future, however, the same amount of tokens can be issued in the newly created mainnet and exchanged 1: 1. This process can be done automatically through the Smart Gateway, described later. Currently, the mainnet of NKCL Bio-Blockchain is limited to private blockchain only.

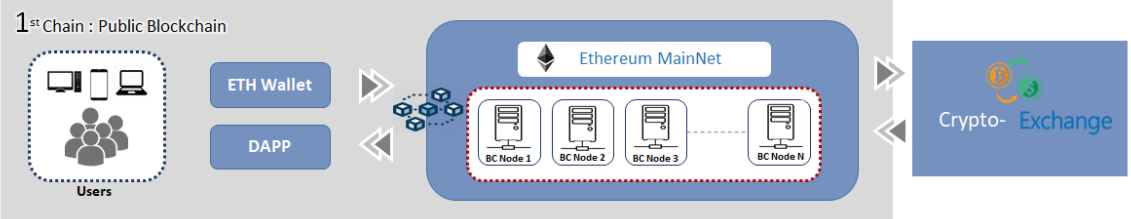


[FIG 4.2. NKCL Bio-Blockchain Architecture(Public Mainnet)]

4.2 1st chain : Ethereum (Public) Blockchain

NKCL Token is basically made of ERC20 Standard of Ethereum Mainnet. This token means that users can transfer tokens between individuals without any restrictions, and can also be freely traded after being listed on the Exchange. In addition, due to the nature of the world's most widespread Ethereum platform, not only personal wallets, but also various wallets on the market, it is easy to manage their own assets, and has the advantage of creating a diverse ecosystem through DAPP development. In addition, due to the characteristics of ERC20, the possibility of technical / business collaboration with other DAPPs of coins is very high.

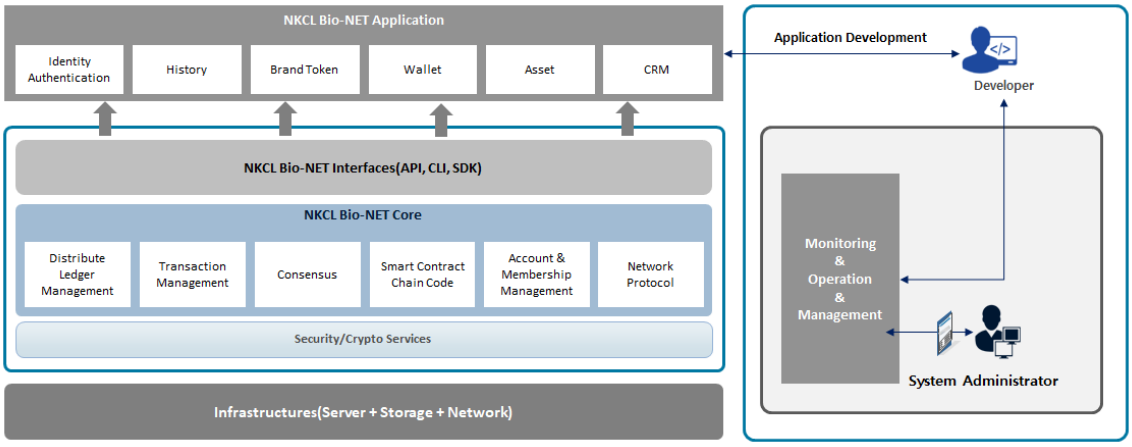
As it is a characteristic of public blockchain, it does not contain personal information, and it is considered as the best platform to guarantee versatility and transparency because the main function is a transaction that operates only with blockchain address value and private key.



[FIG 4.3. NKCL Bio-Blockchain : 1st Chain]

4.3 2nd chain : NKCL Bio-NET (Private) Blockchain

NKCL basically starts from the part related to the culture of NK cells. It will also be used for personal health and other health-related businesses. In this case, there is a high possibility that various pieces of information are mixed and stored, and there are many pieces of information to be protected. In addition, there should be guidelines for storing all information related to the individual such as personal information protection law. Even if all the guidelines are followed, the technical aspects of the most important storage areas will become more important. Blockchain is evaluated as the only solution that can guarantee security and integrity of information. Therefore, in this project, the private blockchain is used instead of the public blockchain in storing such information. In addition, by adopting Hyperledger Blockchain technology, which has the highest utilization of enterprise blockchain on the basis of private blockchain, it will work to increase security and stability.



[FIG 4.4. NKCL Bio-Blockchain: 2nd Chain]

4.3.1 NKCL Bio-NET Application

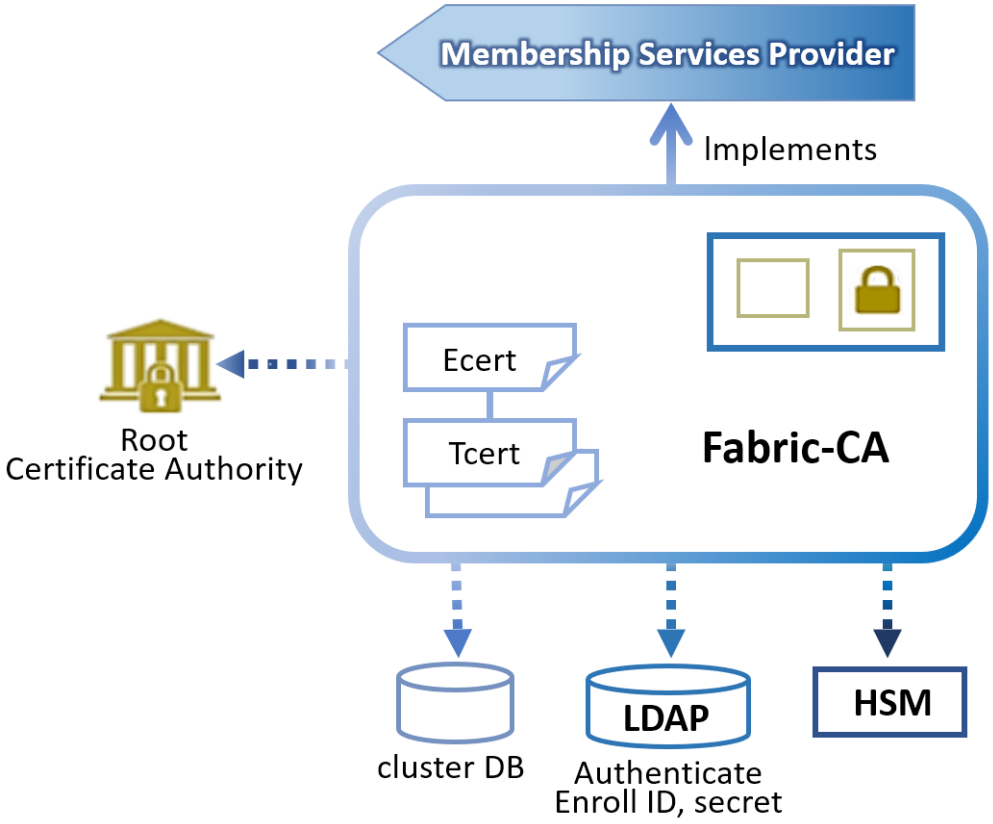
It is an application that implements UI (UX) environment that communicates with NKCL Bio-NET Core. Here, the user can enter and manage various personal information / related information most safely, and various histories (culture history / culture status) can be checked.

Also, the user's membership management, identity authentication, membership management, etc. are also performed. In addition to Key Cryptography, FIDO (biometric authentication) will be used as a two-factor for authentication.

4.3.1.1 Identity & Authentication Manager

This module is responsible for overall tasks such as identification of users accessing the blockchain, authority management, membership management such as membership level, etc.

The basic part is to borrow parts from the Hyperledger Fabric model, and the details will be modified to fit the model.



[FIG 4.5. Authentication Basic]

4.3.1.2 History Manager & Viewer

It is a view implementation and user interface module to show user related information (information stored in blockchain). It is a module that provides the user to search his / her token usage history (token deposit and withdrawal, brand token conversion and usage history, donation history, etc.).

In addition, a management module for managing user information is provided to allow an administrator to control functions.

4.3.1.3 Brand Token Manager

This module is a management module that plays the role of creating and issuing transactions, increasing the issuance, and burning of brand tokens for individual brand tokens of NKCL Token.

In Ethereum's method, contracts are created using pure functions or callback functions along with constructors, transfers, and token creations. Once the generated contract is registered, it means that the smart contract is ready to run.

The token manager of this module also provides the above functions, and can control all necessary contents such as issue amount, burn, and property change. Token control on the blockchain is only through this module. In blockchain core, the corresponding chaincode is created, and the chaincode call of the function action activates the corresponding function.

4.3.1.4 Wallet Manager

The NKCL token used in the NKCL Bio-Blockchain exists as a medium used in various bio businesses as well as NK cell culture. In addition, it is necessary to issue brand tokens in order to solve the inconvenience caused by the differences in business areas.

Brand tokens are tokens that are specific to each business area, apart from the NKCL tokens, which are used as the main exchange medium. In other words, the NKCL token is used as a common means of exchange, and each business brand token exchanged with the NKCL token is used exclusively for the purpose. For example, there may be a brand token used for the sale or use of anti-aging products.

Each business entity will create a wallet for each business purpose and store each brand token as well as NKCL tokens. Wallets can exist in a unified form or can be created separately for each business.

Brand tokens are used for a limited purpose but can also be used as a reward to suit the purpose of the business. After the exchange with the NKCL token through the NKCL Bio-Smart Gateway in the wallet, you can trade through the Exchange.

Therefore, individual wallet address should not only exist NKCL but also exist by brand. The only difference is that for KYC, only one is issued for each type, but it can be issued in multiple cases only in special cases.

The module that creates and manages these wallets is the wallet manager, which is also linked to the chain code of NKCL Bio-NET. The method of management is predefined in advance and the number of tokens is not limited.

4.3.1.5 Asset Manager

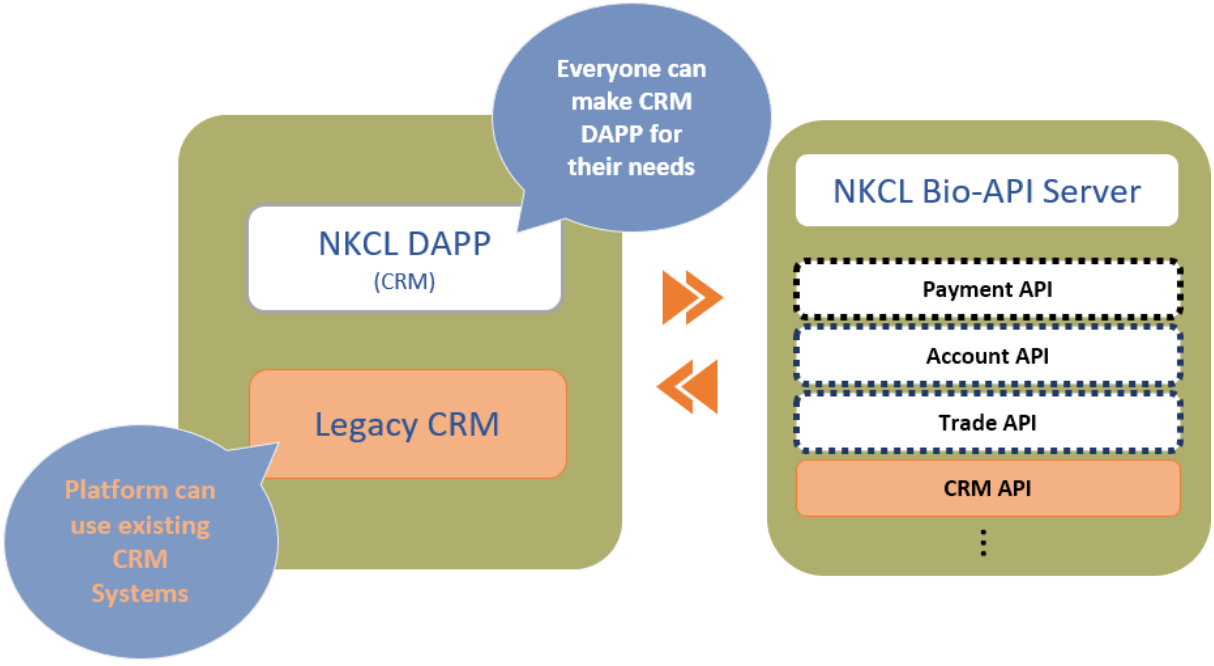
Assets are tangible or intangible digital assets that can be recorded and used on the blockchain, such as cryptocurrencies or tokens, real estate, insurance, licenses, copyrights, loans and collateral, which are the means of storing value.

In addition to cryptocurrency assets, various types of assets such as bonds, securities, and derivatives can be digitized and recorded and stored on the blockchain. Based on distributed ledger technology, assets will meet blockchain, which is a combination of cryptography, data structure, and P2P technology, and will be used as a medium of exchange as well as a value storage means that constitutes the blockchain ecosystem with the advantages of transparency, security, and immutability. Currently, only tokens are used, so this will not be useful for the next few years, but this module is useful when the direction of business is to deal with various assets including real estate. However, for the future, we decided to introduce it into the architecture.

4.3.1.6 CRM

C / S work related to customers can record or record according to the Personal Information Protection Act, and store it according to the guidelines. As a module that manages this, the customer response work that is performed externally is done outside the blockchain and stores only the data part to be recorded and left in the blockchain using the CRM module. Basic customer service is carried out in customer center (traditional customer service area)

by external API of Smart Gateway, and the process and results are managed in blockchain. It is also a part that can increase customer satisfaction by transparently processing without any doubt about preservation of records or forgery of data itself.



[FIG 4.6. NKCL Bio-NET Application & CRM]

4.3.2 NKCL Bio-NET Core

This is a core part of the private blockchain, the mainnet of the platform currently being built, and is the basic platform that handles all important data. As it adopts blockchain based on Hyperledger, the construction period is short and it can make business area naturally

unlike blockchain that builds existing mainnet. It can be easily expanded to various areas, and it is easy to solve when a problem occurs due to the presence of many experts. Also, another strengths is that there is a global company that builds a business platform based on Hyperledger.

In the case of NKCL Bio-NET, the token function is included in the blockchain in addition to this part, and it is also useful for managing various information along with membership management of KYC members.
Due to these characteristics, security is very high compared to the existing blockchain.

4.3.2.1 Blockchain

As the basis for forming a private blockchain, the basic method adopts and uses Hyperledger. Hyperledger has been proven for many years in reliability and stability, and has been adopted by many of the world's leading companies, including IBM, the American Association of Insurance Services, Microsoft, Google, Amazon and Samsung. As this technology becomes more commonplace, so does the number of technicians and the number of companies that make up a common ecosystem with companies that build related applications. The use of Hyperledger in NKCL Bio-NET makes it possible to easily and diversify business support in technical support.

In particular, if the NKCL project grows, it will not bring technical limitations that it will be difficult for the blockchain to link with other projects.

4.3.2.2 Documents

This module stores and manages all information files uploaded by users, personal information, and the results that accompany NKCL projects. This module contains basic document security mechanism, so that forgery of documents is blocked by blockchain technology.

Depending on the size of the information to be stored, the location to be stored may be specified differently.

In particular, if a large file is stored, it will be stored in a special repository, and in this case, the IPFS (Interplanetary File System). Initially, the type of data to be stored is limited and small in size, so there is little need, but as the business expands, the type and amount of information required increases, so external storage is necessary. The Ethereum platform uses SWARM, a decentralized storage, whereas NKCL Bio-Blockchain uses IPFS (a distributed storage file system that can serve with continuity even if the nodes that make up the P2P file system are disconnected, and uploaded files are remembered forever) as a distributed storage system.

Other documents are stored in NKCL Bio-NET and the TxHash is also recorded and stored on the blockchain. TxHash of files stored in IPFS is also stored on the blockchain, so it is easy to check the integrity in the future.

4.3.2.3 Central DB

Basically, blockchain uses distributed ledger, and this module has centralized DB of hybrid type to solve operational efficiency and performance issues.

As everyone knows, there is a gap between the time that a transaction takes place and the time to confirm that it takes a long time to complete a transaction. Many attempts (PoS, DPoS, etc.) have been made to achieve this, but there is no proven and unique position in the market. Therefore, this project decided to adopt the hybrid method with the blockchain, taking advantage of the existing legacy system over other methods that take time to be verified. Of course, blockchain is used to store basic transactions, but it is judged that it is best to use existing legacy system in terms of ensuring convenience and speed when using it for inquiry, summary, and second judgment about records.

4.3.3 Certificate

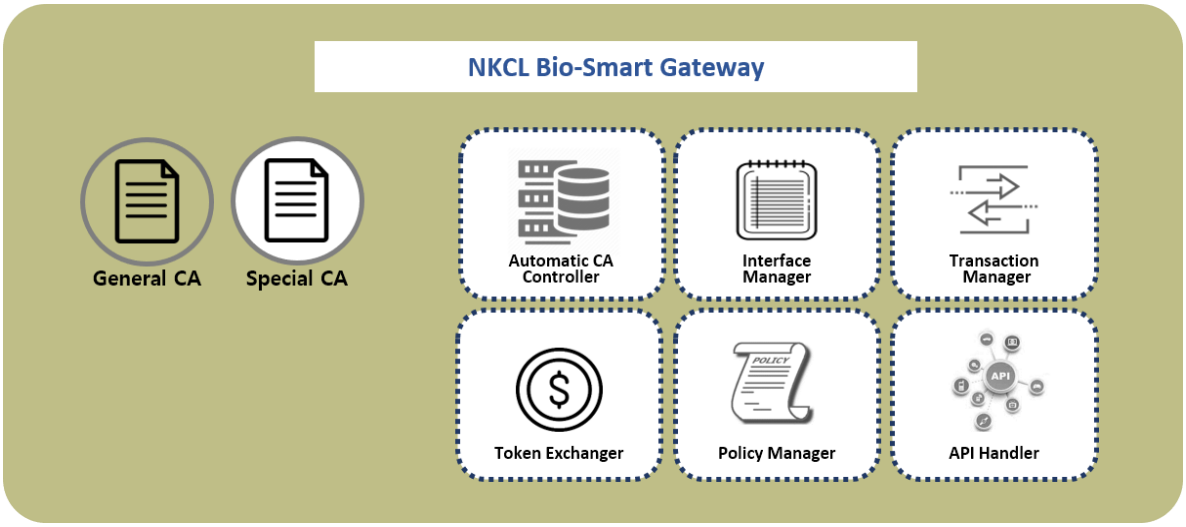
This module manages various certificate issuance and records.
For example, when a premium is discounted through preventive activities through NKCL, it is a module related to issuance of various certificates and copies of insurance, such as discounting or claiming premiums through linkage with insurance companies. It is also provided as an interlocking module required for claims. As the blockchain tertiary industry develops, it is the most useful module.

4.3.4 Verification

This module checks and verifies the integrity of data and transactions. NKCL Bio-NET has a wide variety of business areas and stores a lot of data. So it is almost impossible to check all this data manually and check its integrity. Therefore, it is essential to automate this process to verify integrity. This module is basically used to store and view data.

4.4 NKCL Bio-Smart Gateway

Smart Gateway will not only serve as a bridge between public blockchain and private blockchain, its main purpose, but also to exchange NKCL tokens with brand tokens and externally. To this end, it consists of various modules, including Automatic CA Controller, which acts as a smart contract program. In addition, it should have various interfaces like the role of a gateway, and includes modules that manage all transactions through the gateway and exchange between NKCL brand tokens. NKCL Brand Tokens use the Smart Gateway. They are easily swapped with NKCL Master, the coin required to enter NKCL platform. This method raises the need for NKCL and its various business fields, and lowers the barriers between NCKL Platform and the Brand Tokens.



[FIG 4.7. NKCL Bio-Smart Gateway]

4.4.1 Automatic CA Controller

Smart Gateway has a controller that can perform the same function as a smart contract inside, and handles various transactions in NKCL token. Existing smart contracts have programming limitations because they rely only on the transaction itself. However, Controller in Smart Gateway is programmed as Server-Side Contract including existing transaction and performs various actions automatically. For example, depositing NKCL in a user account (General CA) in Smart Gateway automatically records the transaction in NKCL Bio-NET. If you specify an action after depositing, you can execute various smart contracts, such as the action being executed automatically.
In addition, when depositing NKCL token in the user's special account (Special CA), the specific brand token will be automatically swapped out and issued. Or, if you open a virtual account opened to purchase a specific product and deposit NKCL tokens or brand tokens, you will execute a smart contract that will proceed with the automatic purchase process. You can create a new smart contract or modify or delete an existing smart contract. Business-Oriented Programming can be used as well beyond the existing smart contract. The storage of contracts is done simultaneously to the internal database and NKCL Bio-NET, and has an automatic verification mechanism to ensure integrity.

4.4.2 Interface Manager

It is a part that makes standardization in all interworking related to NKCL Bio-Blockchain, and provides Base Module Interface in consideration of security, convenience of development and scalability.

By defining standardized interfaces of each module, providing basic protocols for internal and external interworking of gateways including protocols, and preparing standardized interfaces, various APIs can be freely created.

4.4.3 API Manager

It is an externally provided module that manufactures and provides technical elements necessary to access this platform in related industries such as payment module, identity

module, membership module, etc. Even if the same payment module has different functions or access rights, another module is provided. Even the same module is provided with a customized module according to the security level of the related company.

4.4.4 Policy Manager

It is divided into parts that set policies related to Smart Gateway operation and parts that can manage brand tokens at a higher level.

Brand token management is a module that defines and manages the exchange rate from NKCL token and brand token. 1: 1 exchange with each brand token is not allowed by policy and can only be exchanged through NKCL tokens.

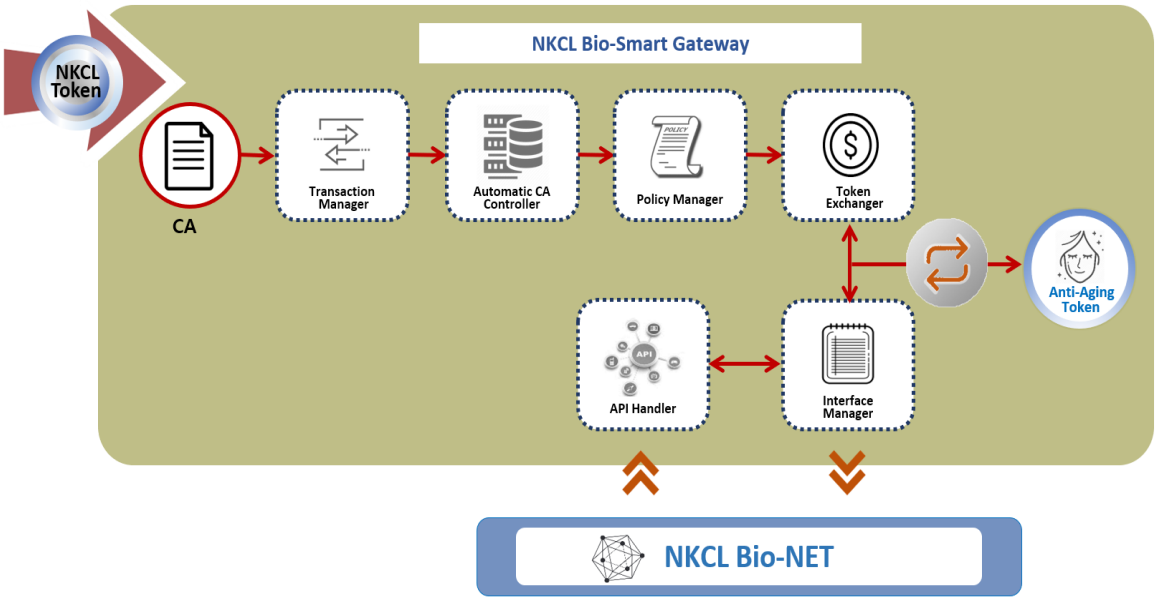
In addition, it provides a part to manage smart contracts related to policies. It is a module that manages various specific contract conditions for exchanges, not a simple exchange policy for tokens, and designates and manages the following actions to be performed during transfers and exchanges as contracts rather than simple token transactions.

4.4.5 Token Exchanger

This module allows you to deposit NKCL tokens and exchange them automatically or manually with the desired brand token, and has a separate external UI.

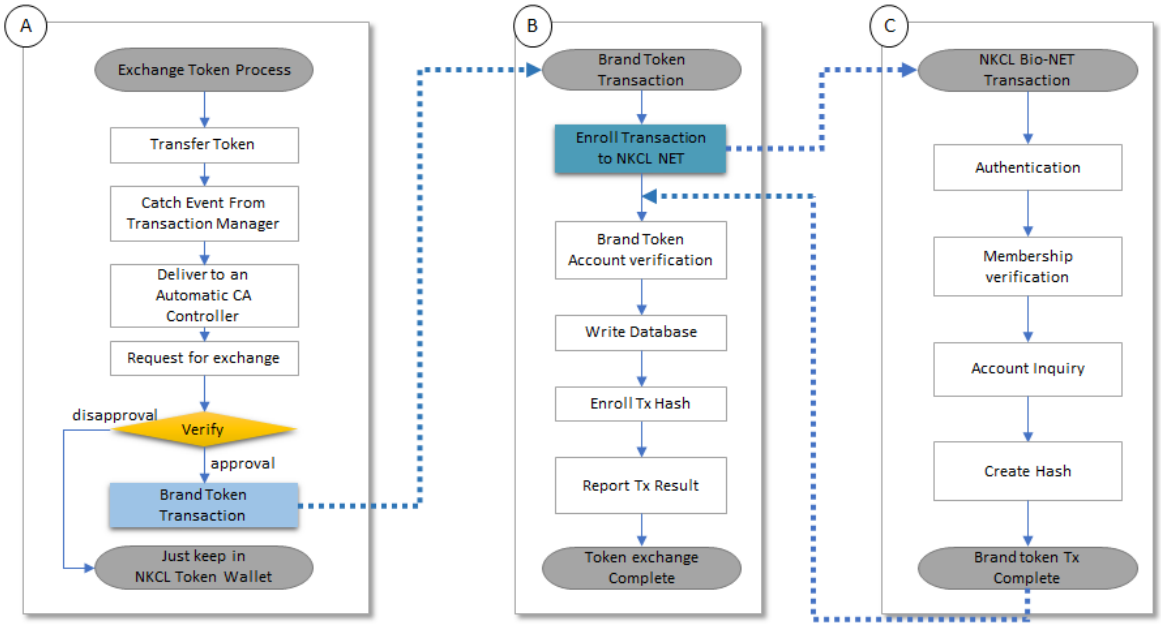
On the other hand, if you want to cash your brand token, you can convert it to NKCL and transfer it to your preferred Exchange or personal account. You can also choose between automatic and manual methods.

The token exchange process is similar to coin exchange, but the difference is that the exchange rate is determined by the business value of each brand coin. As the business with a certain brand coin is activated, the brand value increases and thus the exchange rate with NKCL tokens increases.



[FIG 4.8 Token exchange processes]

Token exchange process is performed after the modules exchanged with token exchange inside Smart Gateway interact with each other and interwork with external Bio-NET as shown in the above figure. The detailed linkage process takes place according to the flow below.



[FIG 4.9 Flows of token exchange processes]

* **Brand Token** (refer to 5.2 Brand Token)

The NKCL token is basically at the bottom of the basic ecosystem of the NKCL blockchain platform, and thus creates various uses depending on the business being created. It will be used to advance into various businesses such as basic cell culture, anti-aging, cosmetics, dietary supplements, and healthcare. The use of NKCL tokens in various business areas is very positive, but as the business grows, it may be inconvenient due to the unevenness in size and profits of each business area. Accordingly, NKCL tokens issue brand tokens separately according to their business and take them into the ecosystem.

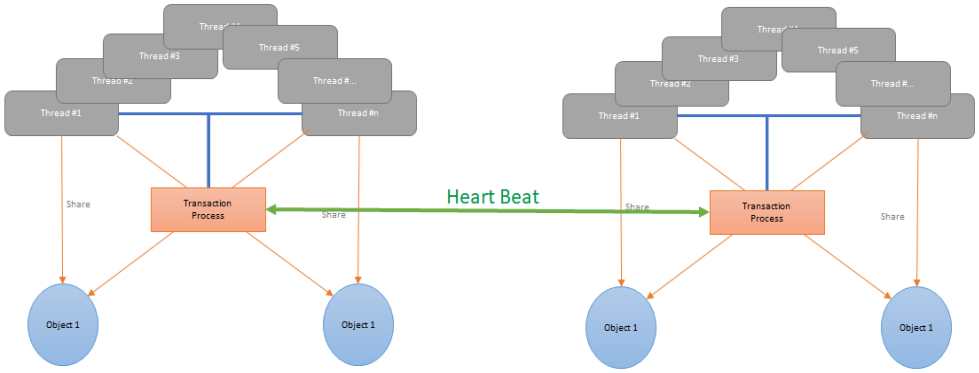
Users can use various anti-aging clinics / products by exchanging acquired NKCL tokens for anti-aging tokens through the Smart Gateway. Users can also receive rewards from the business, which can later be exchanged for NKCL tokens and then cashed in the Exchange.

As the utilization of brand tokens grows and the business scale grows, transaction management will be carried out so that they can be separated into separate tokens.

The Smart Gateway includes an Automatic CA Controller that acts as a smart contract, allowing the user to automatically acquire brand tokens by simply depositing them and controlling them manually.
We can also consider listing the brand token on the Exchange to make it a separate, independent token.

4.4.6 Transaction Manager

This is a module that manages the record of all transactions (in this case, not the record of buying and selling goods, but the behavior when various events occur). The transaction manager has a multi-threaded structure based on the role division and shares basic internal resources of the server. In addition, the physical configuration of the module is formed to enable the HA configuration for stability.



[FIG 4.10 Multi-Threaded Transaction Process]

4.5 NKCL Bio-API Server

It is an interworking module of NKCL Bio-Smart Gateway and a module that performs direct connection with many internal / external modules. Since it is exposed externally, it should be less likely to be bugged, and it should be linked with a number of companies and programs. Since this API server cannot contain all the functions, it is necessary to include the API parts essential for blockchain and ecosystem among them.

4.5.1 Payment API

As an API related to payment part with external module, it supports both direct and indirect payment methods. In the future, it will also support the PG (Payment Gateway) method required for interworking with credit cards. It is one of the highest priorities when implementing an early platform. In fact, to activate the blockchain ecosystem, it's a good idea to apply techniques that are more likely to be used by more users. In that sense, the module on the payment side is useful everywhere. Rather than simply providing an API that uses tokens as a payment method, developing an API that performs payments and exchanges at the same time is a shortcut to revitalizing the blockchain ecosystem. Accordingly, this blockchain project will determine the scope of implementation of the API after fully considering it in the implementation.

4.5.2 Account API

It is an API that handles various types of members' external needs in a more secure manner and can be applied collectively according to the security policy across platforms. By presenting standards related to authentication, a variety of external ecosystems can be created.

4.5.3 Trade API

At present, there is no transaction part inside the Smart Gateway. There is only a function for exchanging brand tokens through NKCL tokens, a function for NKCL tokens to be used externally, and a function for interworking with external exchanges.
In the future, as the NKCL ecosystem is activated, the use of each brand token will be high, and the independent character will be strengthened. Smart Gateway function can be extended or transaction function can be entered into Smart Gateway submodule. This API acts as an API that performs the function.

4.5.4 CRM API

As an API for customer service, it will integrate and manage various future businesses. By enabling Single-Sign On, you can integrate and manage the logins of affiliates or affiliated companies of the NKCL platform, and manage all customer management that takes place in one place.

4.5.5 Exchange API

As the NKCL business grows, the number of exchanges listing NKCL tokens increases, and this API is provided when doing direct or indirect business with each exchange. It will be able to exchange tokens and sell / buy in real time with Exchange.

Currently, most of the Exchanges are open to the OPEN API, adopt a python language that is more accessible to programming languages, and support the data transmission format in json format rather than xml. Therefore, this API will also provide OPEN API to be compatible with this, but will be issued only to companies that are authorized to issue keys or trusted individuals and organizations. Existing Exchange API has a security flaw that individuals can be issued a key by simple social media authentication.

4.6 NKCL DAPP

This part is a DAPP for the NKCL ecosystem that is different from the DAPPs of the existing Ethereum ecosystem. In this project, we plan to implement e-commerce DAPP for the successful launch of the project, and open up the results of the implementation so that more developers can participate. We also plan to lower technological, timely and costly entry barriers for companies seeking to work with NKCL.

4.6.1 Cosmetic DAPP

The first pilot-type DAPP to be implemented in the NKCL project was named Cosmetic. It is expected to have the most applications, and the related industrial fields are also very developed, and if activated, the related industries can be developed at the same time. Integration with the NKCL blockchain is based on the basic business, and there are no restrictions on the business areas covered.

The kind of work that can be done in DAPP will also ensure the autonomy of the operators. We will place restrictions on the APIs that work with DAPPs to limit the factors that pose a risk to the blockchain or cause NKCL problems.

4.7 Interactions Among NKCL Bio-Blockchain Modules

The platform consists of several components. They are designed to move in an organic way, and their own daemons are driven by independent processes to ensure their independence. The interaction between each module is as follows.

4.7.1 NKCL Bio-NET & Smart Gateway

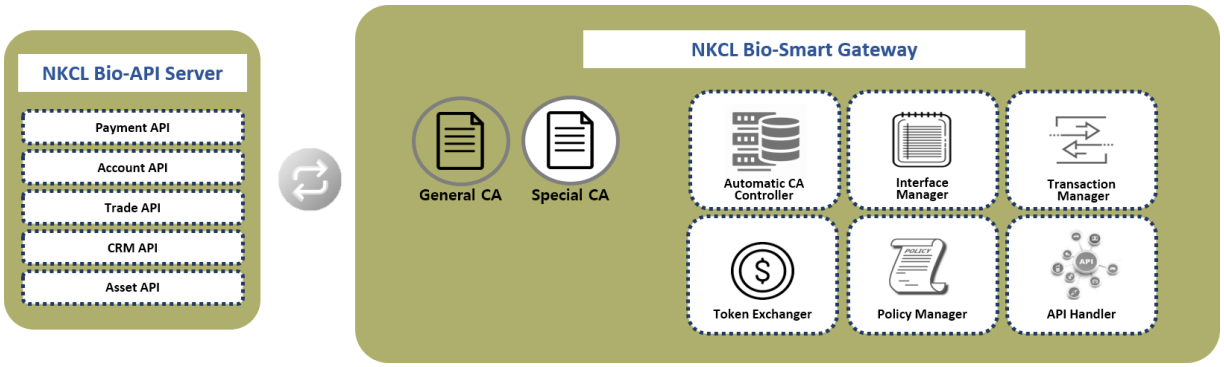
This part has many security-related parts, so the technical part will be omitted.

4.7.2 API Server & Smart Gateway

API Server and Smart Gateway communicate using encryption protocol. It encrypts the contents included in the protocol as well as the secure protocol of the network layer. This is to make the internal data invisible even if the external protocol is hacked from outside. The difficulty and complexity of the protocols does not increase the level of security. The protocol is designed to be as simple and extensible as possible, and the rest is to use specialized security protocols.

On top of this, the API server is implemented to solve the smart gateway and mainly all

business logic. In addition, there is a hidden internal API that communicates with NKCL Bio-NET. This part is omitted for security reasons.



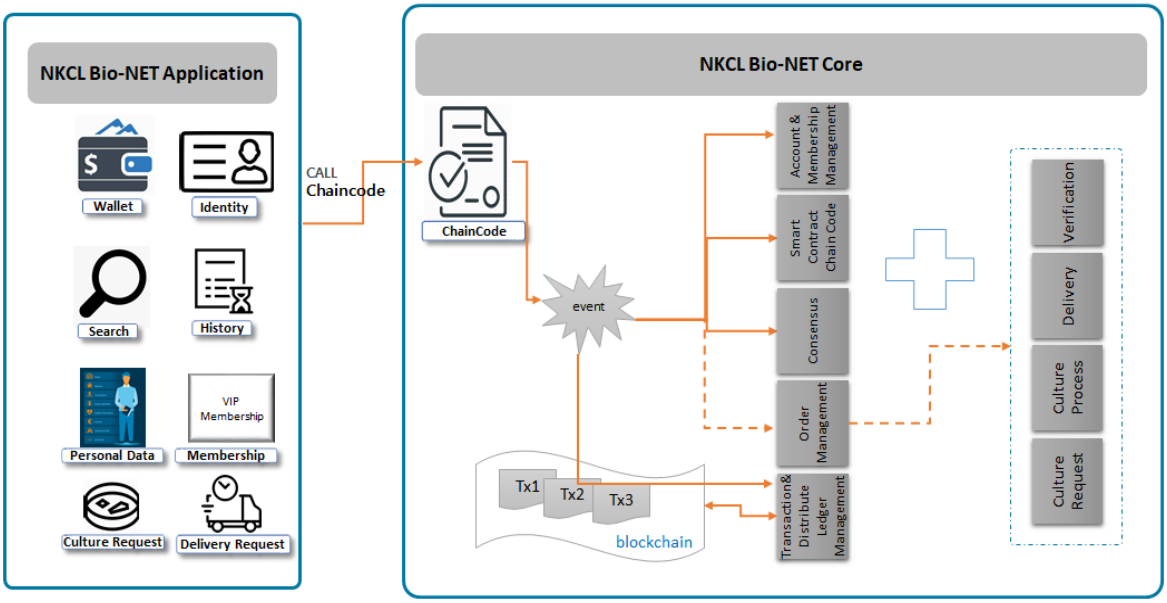
[FIG 4.11 Interaction between NKCL Bio-Smart Gateway & API Server]

4.7.3 Ethereum & Smart Gateway

Interworking between Ethereum platform and Smart Gateway means that Smart Gateway unilaterally conforms to the protocol of Ethereum platform. It would be nice to cooperate with the Ethereum Foundation, but as it is already widespread worldwide and there are many users, it is realistic to see that no separate technical development work for interworking is done.

4.7.4 Bio-NET Application & Core

This part includes the blockchain core, the application that manages it, and the part that includes and manages the business logic of the NKCL platform. The outline is shown in the figure below and the detailed description will be omitted for security reasons.



[FIG 4.12 Interaction between NKCL Bio-Application & Core]

4.7.5 NKCL DAPP & API Server

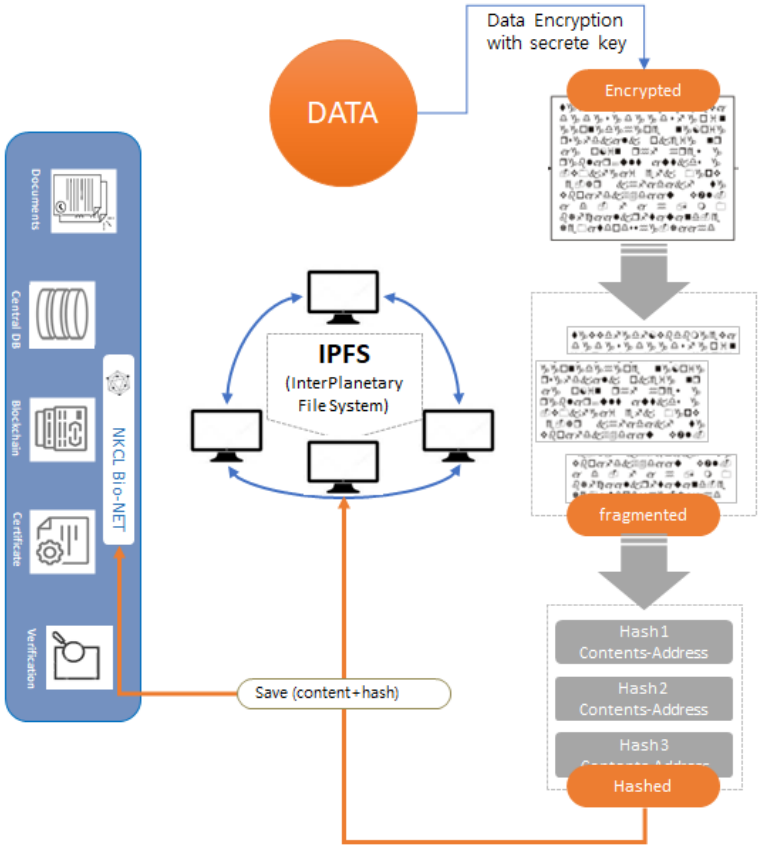
Important modules in the token ecosystem of the NKCL project are DAPPs and API servers. In case of API that wants simple function of Viewer, it can be used by anyone using simple HTTP Secure level protocol or encryption in REST API rather than internal data encryption.

In the case of converting the enterprise solution to DAPP, there will be a standard protocol inside the enterprise, and thus the protocol customized to the enterprise standard will be used.

To make the ecosystem of the DAPP part well, you have to adapt most of the environment to the platform at first. After that, as the platform grows and the number of users grows, the related DAPPs meet the standards.

4.8 IPFS (Distributed Storage File System)

Basically, the type and size of the data coming into the NKCL Bio-Blockchain is determined. When small data of less than a certain size comes in, it is stored in the basic blockchain of NKCL Bio-NET. If the size is exceeded, the data is stored using the Distributed Storage File System. Distributed storage file systems such as IPFS have the advantage of restoring files even in the event of a hardware failure without a separate backup server. In addition, by decentralization, the storage and retrieval speed is fast and the load can be handled flexibly. By recording the TxHash stored in this distributed system back to NKCL Bio-NET blockchain, it is possible to check and confirm any IPFS system error or file forgery.



[FIG 4.13 Using IPFS as a storage for big data]

NKCL·M
NKCL MASTER

TOKEN ECONOMY

5. Token Economy

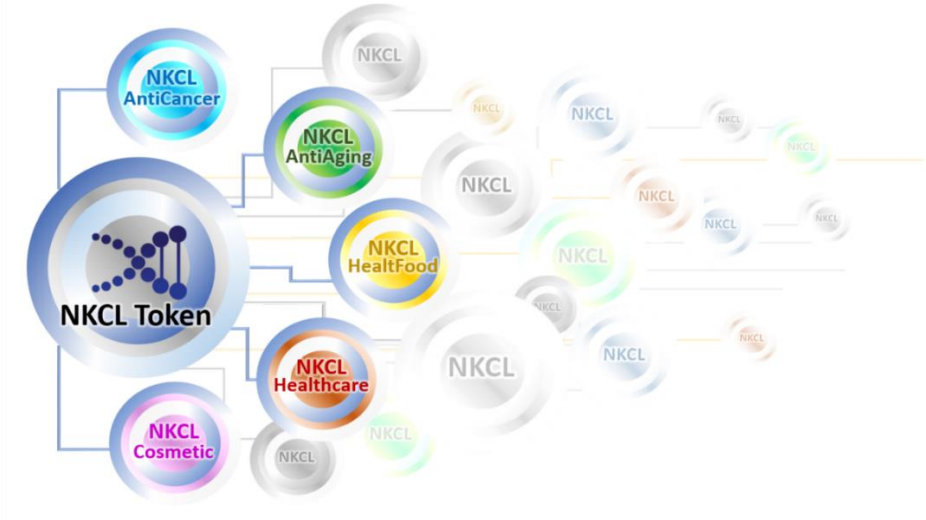
The term Token economy usually includes rewarding blockchain members or participants to activate the blockchain itself and even the governance area of the distributed ledger. It also refers to a series of ecosystems that provide multiple services using tokens used in the blockchain and generate profits.

5.1 NKCL Token

Tokens can be divided into utility tokens and securities tokens, which are means of goods and services. Among these, securities tokens require a careful approach due to differences and regulations in each country's legal system and qualifications that deal with securities. We want to define NKCL tokens as utility tokens by their purpose or usage.
NKCL token refers to usable tokens by combining blockchain and ecosystem, utilizing personal health data and tokens such as usage history, culture history, and clinical results, and executing immune cell therapy, the high-tech biotechnology.
In general, various medical institutions and pharmaceutical companies will be able to contribute to the medical development by utilizing the medical data, such as telemedicine, healthcare, clinical trials. In the NKCL Bio-Blockchain, the user has a reward system that contributes to the virtuous cycle of medical development and culture by providing his own health-related data and receives NKCL tokens as a reward.

5.2 Brand Token

NKCL tokens can be used as a common exchange method in various NKCL ecosystems such as affiliated hospitals, anticancer centers, anti-aging centers and shopping malls. It functions as a utility token that is a means of exchanging goods and services.
However, each business may need a limited purpose token that can be used separately from the NKCL token, which is called a brand token. Brand tokens can exist for each business area and can be created in more detail according to needs and purposes.
For example, there may be NKCL-Cosmetic and NKCL-AntiAging brand tokens for cosmetics businesses and NKCL-HealthFood brand tokens for bio food businesses.



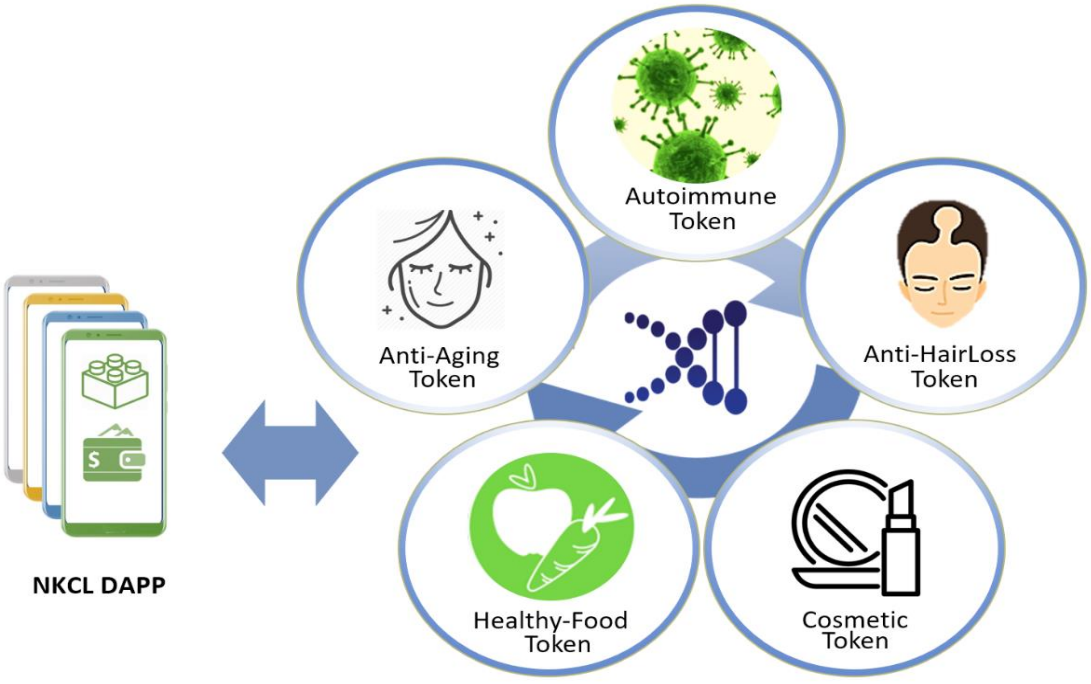
[FIG 5.1 NKCL Token & Brand Token]

5.3 Token Ecosystem

The token ecosystem is a token-based common fate created by the Token Economy. The ecosystem is based on the premise of interaction among members, which creates synergy according to the influence of each other. As a complex with interdependencies around tokens, it is the basis for continuous production and collaboration.

Because the token ecosystem is a token-based organization, token distribution, rewards, and efficient management systems are essential and based on behavioral economics.
Through smart contracts, not only customers but also evaluations, rewards and assets of business entities can be managed independently without a central entity through tokens.
As shown in the following figure, the NKCL ecosystem consists of each brand token to be exchanged around the NKCL token and NKCL DAPP (distributed app) linked with the brand token. The exchange of NKCL tokens and brand tokens is processed in real time through the internal modules of the NKCL Bio-Smart Gateway, and interworking with NKCL DAPPs is via the API interface.

Deposit and withdraw NKCL tokens to the NKCL Bio-Smart Gateway via the Ethereum mainnet. Also, the process of exchanging each token, reward, inquiry, etc. is done through smart contract, and the result is stored in NKCL Bio-NET's private blockchain.



[FIG 5.2 NKCL Token & Brand Token]

For example, business-specific brand coins such as NKCL-Cosmetic, NKCL-Healthcare, NKCL-AntiAging, NKCL-HealthFood, NKCL-BioChemical, and NKCL-Autoimmune can be generated as shown in the figure. NKCL Master is NKCL's major Brand Token that is used for purchasing other NKCL Brand Coins that are specialized in each business fields.

5.3.1 What is NKCL Master?

NKCL Master is used for entering NKCL Platform and it is exchanged with other different NKCL Brand Tokens that are used in various business fields. NKCL Brand Tokens that are exchanged with NKCL Master, are used for their own purpose in their respective business fields.

5.4 Token Reward

There are various ways for users to receive rewards on NKCL Bio-Blockchain.
The easiest way to earn rewards is to use NKCL tokens and their brand tokens. It is as if we buy something at the mall and get reward points. Likewise, when NKCL brand tokens are consumed in the corresponding DAPP, rewards are given to users by using various indicators such as the amount of consumption and the frequency of how often they are used.

In addition, the user can also be rewarded by providing data on the results of the NK cells culture and application, and information on the types of medicines taken before the culture and the physical condition (how much exercise, what foods, etc.). This part will go through personal identification / de-identification process to keep the data and decide whether or not to provide the information.

① When the user uses the token or purchases an item using the token,
② the user is rewarded for using the token.
③ The user's history is organized by specific period (weekly / monthly, etc.)
④ and automatically settled by period according to the token reward policy.
⑤ The token reward policy is very simply set up and executed.

예) If the use amount of Cosmetic Brand Token in unit period is
1500 NKCL-C → 3% Reward,
3000 NKCL-C → 7% Reward,
5000 NKCL-C → 12% Reward

[FIG6. Token Reward Calculation : Using Brand Token and Purchase]

① Graph the weight of upload count of all user data * uploaded data in chronological order

② Standardize through normalization of graph

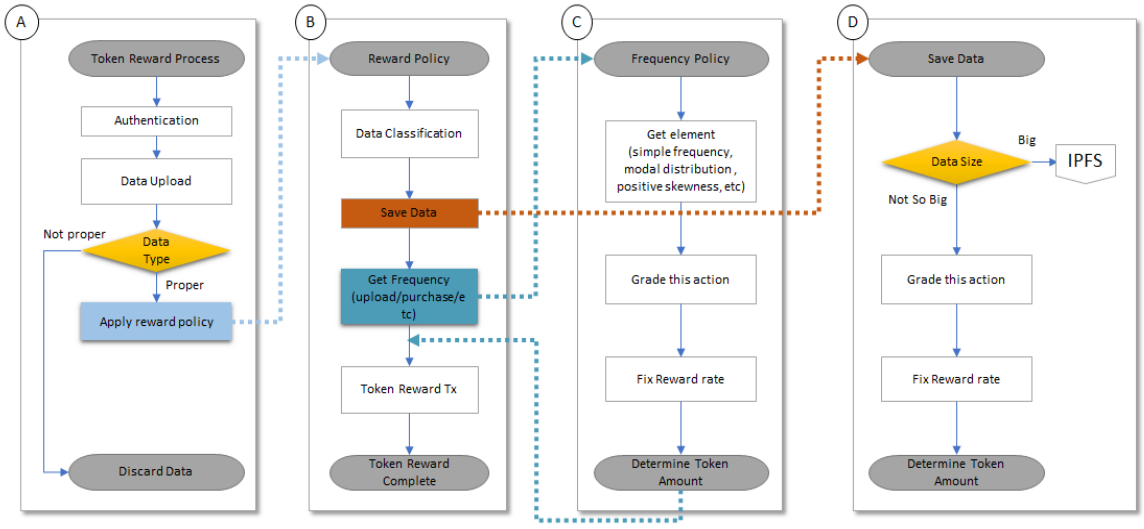
③ Standardize the data of individual users through the above process

④ Apply skewness, modal, and kurtosis of individual users to reward policy of users

⑤ Convert user's scale to token amount

$$skewness = \frac{\sum_{i=1}^{n}(x_i - \bar{x})^3}{s^3} \qquad kurtosis = \frac{\sum_{i=1}^{n}(x_i - \bar{x})^4}{s^4}$$

[FIG 5.3 Token Reward Calculation : Data Upload]



[FIG 5.4 Token Reward Process]

① Information provider reward plan

As the quality of information and the frequency of actions increases, the reward policy is applied differently to increase the motivation of providing information.

② Information consumer reward plan

The information consumer can refine the data when it accumulates on the NKCL platform in the future and improve the quality. In this case, with the consent of the information provider, the information consumer will receive a token in exchange for the appropriate information provision, and a policy for distributing it back to the information provider will be prepared.

③ Token user reward plan

Token users (including brand tokens) will be rewarded according to the guidelines presented by DAPP or the project, and the degree of reward will be managed and paid transparently according to the above-mentioned process.

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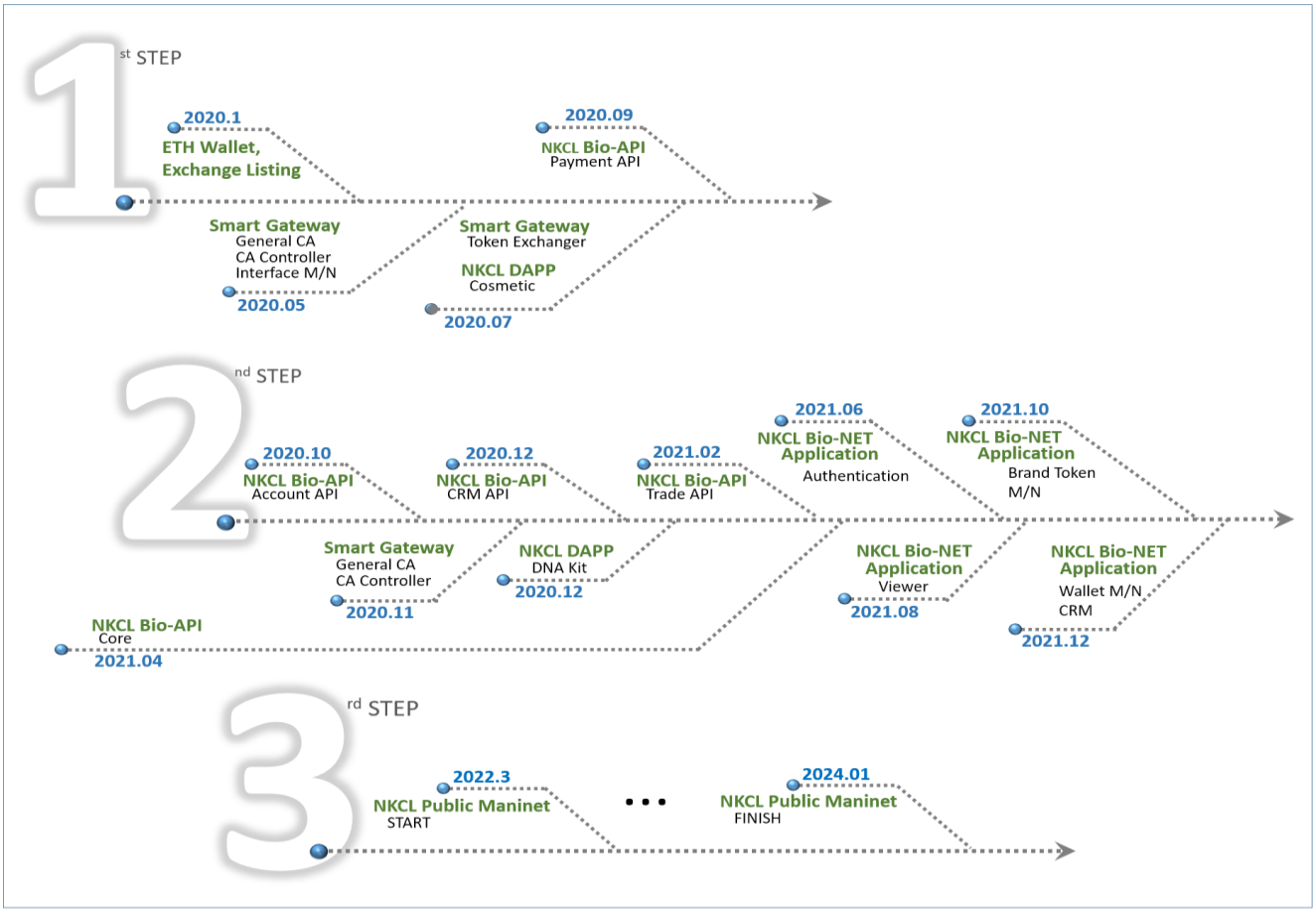
ROADMAP

6. Roadmap



6.1 Step 1: Build a Platform to Create Basic Ecosystem

In Step 1, CA function of Smart Gateway and Interface Manager are mainly built, and Token Exchanger function will be implemented as half-digit function. Once the DAPP and Payment APIs for the ecosystem are built, the basic ecosystem creation is complete.

6.2 Step 2: Build a Platform to Complete Private Mainnet

In Step 2, a mainnet is established to store and manage not only basic user information but also personal information, health information, user uploaded information, and transaction information based on Hyperledger. In this stage, basic functions such as membership management and inquiry function related to members are included, as well as functions such as brand token generation and management.

In this stage, we will also develop an application with Business Logic combined with blockchain. (A platform that can do everything with blockchain itself is not available at present. So, all financial blockchains are being developed by dividing business and blockchain areas.)

6.3 Step 3: Build a Platform to Complete Public Mainnet

The key to Step 3 is to build your own public mainnet instead of the existing Ethereum platform.

The Ethereum platform is a platform that accepts all tokens used by more than 90% of the world, so there may be a problem with the transaction speed. Regardless of this project, if Ethereum has a problem, this project may have consequences, so it may become critical in the future. Therefore, 3 steps should be prepared and performed without excluding this possibility, but the actual performance should be determined after careful consideration.

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LEGAL CONSIDERATIONS AND OTHERS

7. Legal Considerations and Others

The NKCL white paper is intended to document and communicate the overall business plan for the project, not used to recommend specific investments. Please note that NKCL will not be liable for any damages, losses, liabilities or other financial damages resulting from the acquisition of this white paper.

The content of this white paper should not be considered as an incentive or invitation to engage in investment activities. The referee should carefully consider and review all risks, ICOs and other relevant business activities related to cryptocurrencies. No warranty is given or assumed to the referee.

Risk Statement

Regulatory authorities have not reviewed or approved the information set out in this white paper. Such action may or may not be taken in accordance with law, regulatory requirements or rules of jurisdiction.

The publication, distribution, or dissemination of white papers does not imply that the relevant laws of jurisdiction, regulatory requirements or rules have been complied with. To the maximum extent permitted by applicable laws, regulations and rules, Distributor and its affiliates and their respective officers, employees or agents, coins, and related products and services shall not be liable for all kinds of damages, including direct, consequential, incidental, special or indirect damages (Including but not limited to lost profits, lost sales or other damages).

Terms & Conditions

Cryptocurrency coins should not be considered an investment, but they can gain value over time. In addition, if the solutions implemented by NKCL are not actively used in the real world, they may be of reduced value.

The funds recovered during the risk of loss of funds ICO are not guaranteed. In the event of loss or loss of value, no individual or public insurance agent can cope with the purchaser.

In the funds collected during the risk of failure ICO, the various risks that may arise in other companies in the business, such as NKCL COIN business and all subsequent marketing activities end in failure, etc., also apply to this issue.

Technological innovations, such as the development of quantum computers, are potentially dangerous for cryptographic communications involving NKCL COIN.

In the event that the NKCL COIN cannot be used due to the indemnity of warranty or various reasons, the loss is the responsibility of the party who purchased the coin and NKCL will not be held liable for any party.

After the date of issue, NKCL COIN will be sent to the party who purchased it without any warranty, express or implied, without infringing other's intellectual property rights.

Some jurisdictions do not allow the exclusion of implied warranties, so the above exclusion may not apply to you.

Appendix

A. Patent

Increasing survival rate of cell therapy method (Application No. 10-2018-0034464)

Lymphocyte harvesting method using density gradient centrifugation (Application No. 10-2018-003448)

B. Regenerative Medicine Act

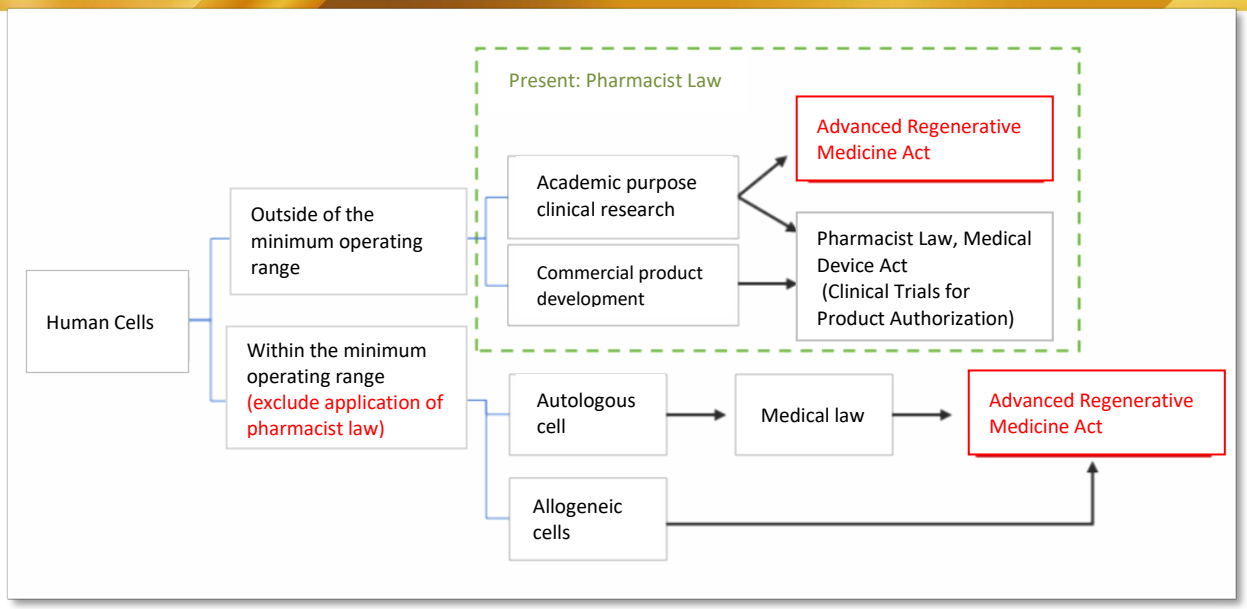
Advanced regenerative medicine is a medical technology that replaces or regenerates human cells, tissues, and organs to restore their original functions, and includes cell therapy, gene therapy, tissue engineering therapy, and fusion therapy. The difference from the existing medicines and medical devices is that living cells have a complex mechanism of action as a main ingredient, and it is difficult to evaluate safety and efficacy in animal experiments and is highly related to medical procedures. Therefore, in terms of licensing, it requires a different classification system from pharmaceuticals and medical devices. In Europe, Japan, and the United States, new definitions were taken into account, and new laws and systems were started.

To date, there are no advanced regenerative medicine laws and licensing systems in Korea, but the necessity has been raised in the 19th and 20th National Assembly. In February 2016, the 19th National Assembly proposed the 'Act on Advanced Regenerative Medical Support and Management', but was automatically scrapped, and the 20th National Assembly issued two legislations related to advanced regenerative medicine by November 2016. Since the legislation was instituted, the media had the view of it being as the infringement of the right to life, safety concerns, and a law of preferential treatment for state affairs. However, most articles in the first half of 2018 raise the necessity of enacting special laws related to advanced regenerative medicine based on the case of Japan and the reality of overseas medical expedition. In the morning of July 17, 2019, the 'Act on the Safety and Support of Advanced Regenerative Medicine and Advanced Biopharmaceuticals (hereinafter referred to as the "Advanced Regenerative Medicine Act")' passed the second legislative committee of the National Assembly Legislative Judicial Commission. This includes the priority screening of biopharmaceuticals for the treatment of rare diseases, step-by-step preliminary screenings tailored to the developers, and conditional approvals to expand treatment opportunities if fully validated.

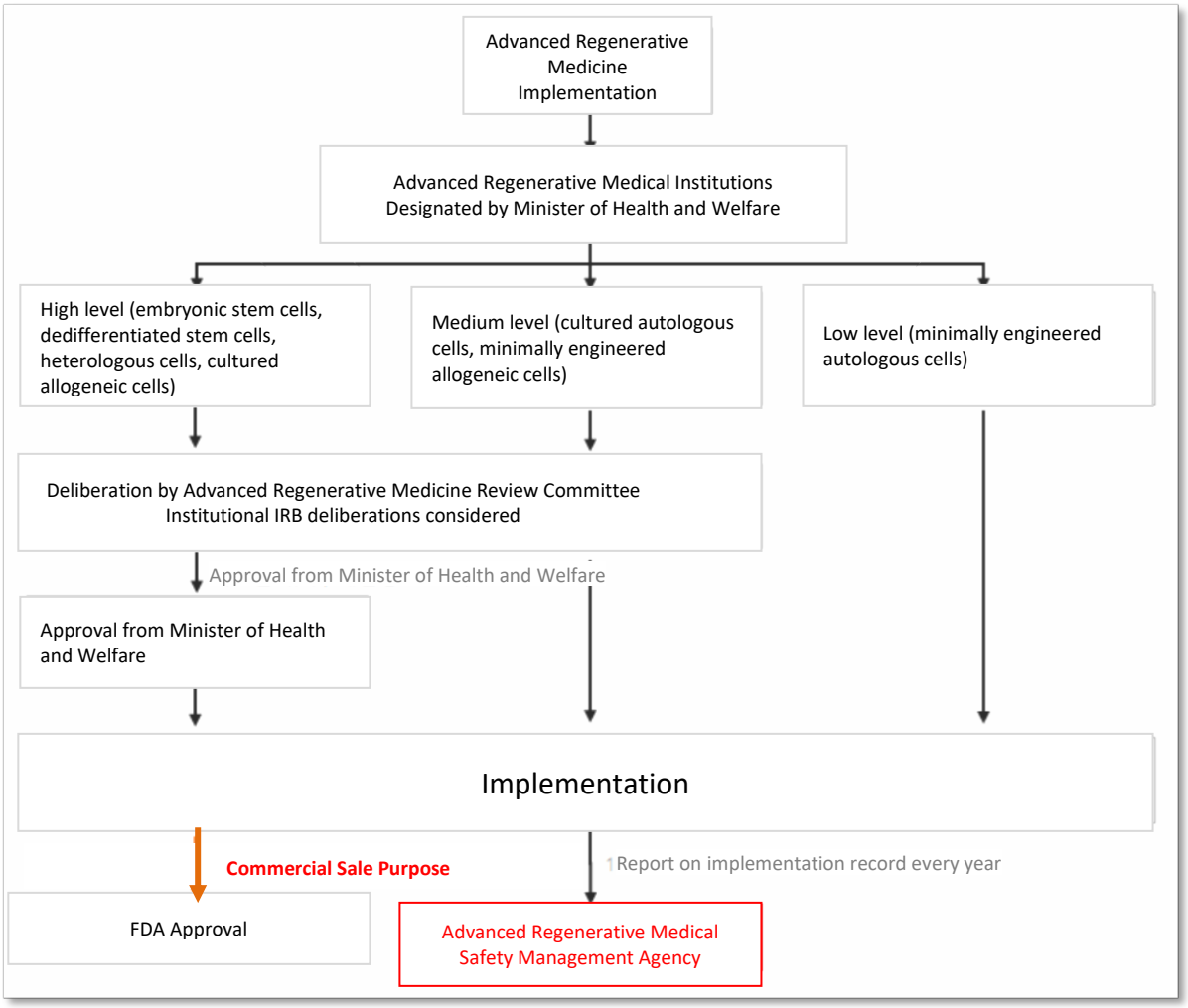
It is proposed to manage biopharmaceuticals and regenerative medicines that have different characteristics from the existing synthetic drugs in separate legislation, like in the US and Japan.

The 'Act on Advanced Regenerative Medical Support and Safety Management' has been revised several times as discussed above. But the gist is to open the way to providing treatment opportunities for patients who have been unable to cure the treatments developed to date. In other words, it is a system to provide regenerative medical treatment opportunities and a foundation for safe treatment in Korea, and to develop therapeutics and promote related industries through clinical research. It also includes support for the development of the regenerative medical industry, a future growth engine at the national level. It is also aimed at promoting the development of regenerative medical products and promoting the mutual growth of infrastructure industries such as cell culture and manufacturing facilities.

The scope of application of advanced regenerative medicine law is set as the clinical research for the regenerative medicine within the minimum operation scope and the research operation outside the minimum operation scope, except for the clinical trial for product approval prescribed in the current pharmacist law and medical device law. Commercial sales are not possible under the advanced regenerative medicine law. **For commercial sale, the pharmacist law or the medical device law should be applied**.



[Advanced Regenerative Medicine Scope]



[Advanced Regenerative Medicine Implementation Process]

C. Types of T Cells

C.1 Naive T Cell

Naive T cells are differentiated and matured but have not yet encountered antigen at the periphery. Upon encountering an unrecognized MHC: Antigen complex present in the antigen-transmitting cell, it recognizes the antigen through the T-Cell Receptor signaling pathway and activates it as an effective T cell, initiating adaptive immunity. On the surface, L-selectin (CD62L), a cell adhesion molecule, is present, whereas CD25, CD44, CD69, which are characteristic of effect T cells, and CD45, which are characteristic of memory T cells, are rarely present.

C.2 Helper T Cell

Helper T cells, or Th cells, are cells that promote humoral immunity by regulating the differentiation and activation of other white blood cells in effect T cells. It is also called CD4 T cell because of its CD4 protein surface. The helper T cells are further classified into Th1, Th2, Th17, Tregs, etc. according to the detailed function. Th1 cells secrete interferon-gamma, IFN-γ, Tumor Necrosis Factor beta, and TNF-β to induce endosomes and lysosomes to form endosomes inside macrophages. Th2 cells, on the other hand, secrete several types of interleukin (IL), allowing B cells to differentiate into plasma cells. Th17 cells secrete interleukin-17 (IL-17) to collect neutrophils [2]. Treg cells, also called regulatory T cells, do not promote immune responses, but rather inhibit autoimmune responses by maintaining homeostasis of immunity.

C.3 Cytotoxic T Cell

Cytotoxic T cells secrete cytotoxic substances such as **granzyme** and **perforin** to kill cells infected with the virus or tumor cells. It is also called CD8 T cell because it has CD8 protein on its surface. In contrast to helper T cells, it mediates cellular immunity to remove viruses and cancer cells.

C.4 Natural killer T Cell

Natural killer T cells are one of the effector T cells which are distributed in a small proportion compared to the helper T cells and the cytotoxic T cells. It has a T cell receptor (TCR) like T cell on its surface, but it also has a natural killer cell specific molecule such as NK1.1. Natural killer T cells secrete gamma interferon, interleukin-4 (IL-4), interleukin-10 (IL-10), and the like to regulate immune responses.

C.5 Memory T Cell

Memory T cells are cells that have a long-term viability after differentiation and screening of antigen-recognized T cells, and are rapidly activated when antigens invade again later, and have the potential to function as effective T cells. . The naive T cells meet the antigen and become active, or effect T cells are affected by interleukin-7 (IL-7) and interleukin-15 (IL-15) to differentiate into long-lived memory T cells.

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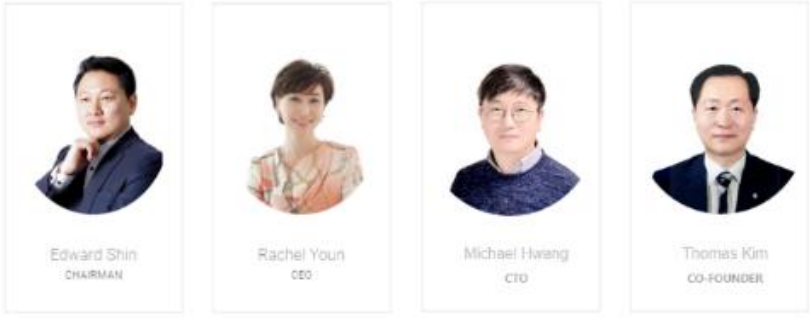
TEAM & REFERENCES

8. Team

CO-FOUNDERS



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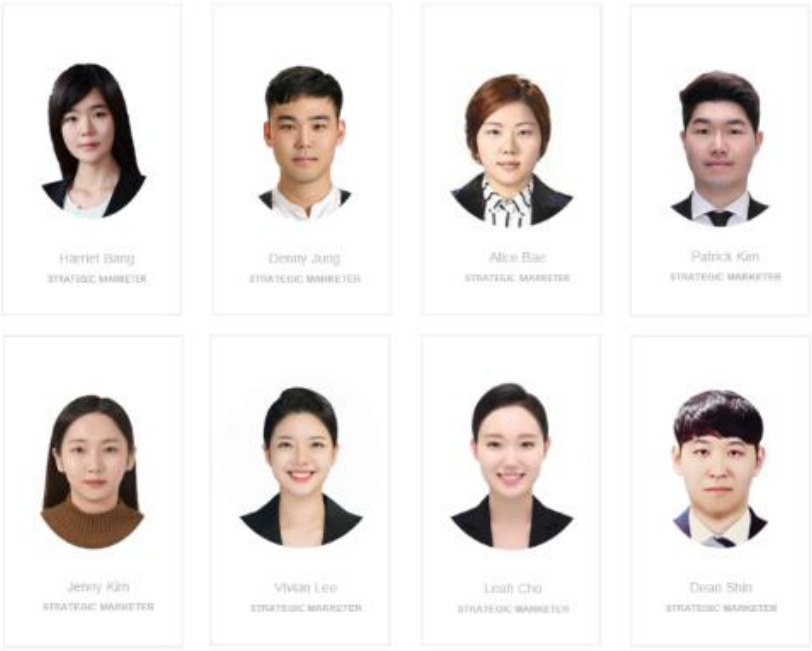

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