LECTINS AND EXOSOMES
— HERALDING A PARADIGM SHIFT IN MEDICINE AND DRUG DISCOVERY —

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SUMMARY

- In the medicine and drug discovery fields, there is a need to relieve the pressure on medical costs[1] caused by the high price of drugs[2] and to eliminate side effects and other burdens on patients. Lectins and exosomes are attracting attention as effective tools to resolve these issues.
- For example, it has been reported that a DDS involving administration of a lectin-anticancer drug conjugate to mice demonstrated an anticancer effect 1,000 times more powerful than that of existing antibody drugs.
- In addition, research is progressing into a DDS in which anticancer agents and other drugs are inserted into vesicular exosomes released from cells in order to safely deliver the drug to diseased cells for treatment.
- A field combining the benefits of lectins and exosomes may become the new frontier for medicine and drug discovery.

INTRODUCTION

The April 2019 report entitled "**Glycotechnology**"[3] explained about **glycans**, which are substances that can be used in a wide range of industrial fields. This report looks at **lectins**, which are proteins that bind to glycans on the surface of cells, and **exosomes**, which are vesicles[4] that are released from cells, and presents the view that a **lectin-exosome-drug conjugate**, which is a drug delivery system (**DDS**) combining the characteristics of lectins and exosomes, will attract attention in the medicine and drug development fields. In addition, this report also explains about lectin-based drugs that make use of the numerous functions of lectins, and about the future development of exosome research.

What are glycans?

Glycans are biological material consisting of "sugars" linked together, and they are referred to as the **third biopolymer** after **DNA (the first biopolymer)** and **protein (the second biopolymer)**. The sugars from which glycans are composed are synonymous with "carbohydrates". The starch contained in food such as rice is also

[1] According to the government's estimate, medical costs in Japan will reach ¥66.7 trillion by 2040, and controlling soaring medical costs is an urgent issue.

[2] Ono Pharmaceutical's immune checkpoint inhibitor Opdivo, renowned as an outcome of the research for which distinguished Professor Tasuku Honjo of Kyoto University was awarded the Nobel Prize in Physiology or Medicine, was initially priced at ¥729,849 per prescription (100 mg: currently ¥174,000), with an annual cost (26 doses) of ¥34,596,874.

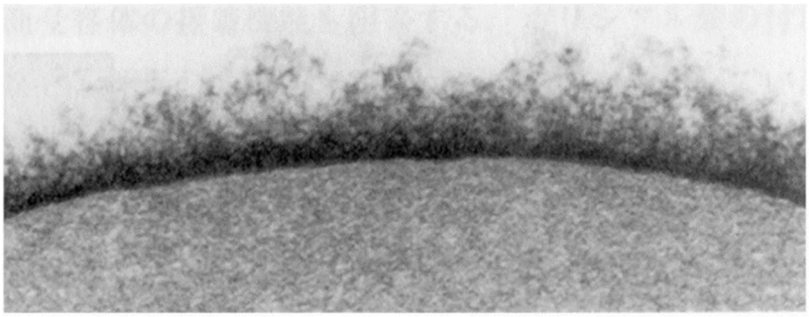
[3] "Glycotechnology", April 2019, Mitsui & Co. Global Strategic Studies Institute
https://www.mitsui.com/mgssi/ja/report/detail/__icsFiles/afieldfile/2020/01/30/1904t_abe_1.pdf

[4] Cells release substances in the body in sacs of various sizes. These sacs are called "vesicles". Exosomes are 30-200 nm (nanometers) in size.

a carbohydrate. This starch consists of a long chain of sugar known as **glucose**, and this glucose is broken down when digested to become a source of energy for the organism. Glucose is a **monosaccharide**, the **simplest form of sugar**, and glycans are biomolecules consisting of long chains of monosaccharides arranged in branched structures[5].

In addition to other biological substances such as proteins, lipids, neurotransmitters, and hormones, glycans cover the surface of almost all cells. They extend outwards from the cell surface like antennas (Fig. 1), and are actively involved in an array of life phenomena by identifying surrounding biomolecules, and gathering and transmitting information by communicating with nearby cells.

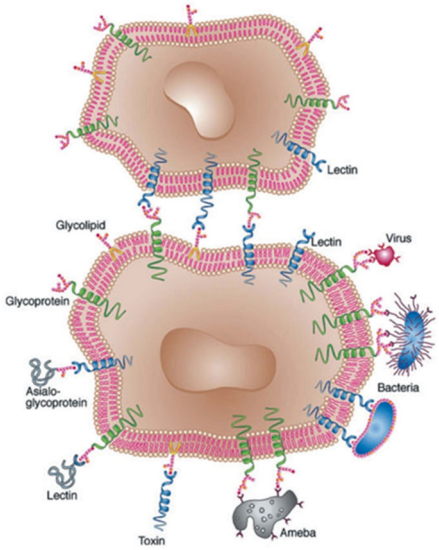
Figure 1 Glycans covering the surface of a cell



Source: Kagaku-Dojin *Introduction to Glycobiology*, p.83

For example, glycans are involved in processes such as reproduction, growth, blood processes, antioxidation, waste removal, immunity, and aging (Fig. 2). Glycans are also used to determine ABO blood types in humans. Human blood is grouped into the four blood types A, B, O, and AB, based on the differences in the glycans on the surface of the red blood cells. In addition, pathogens such as influenza viruses and coronaviruses are able to enter cells and replicate themselves by tricking the glycans protecting a cell's surface into allowing them in using a specific protein called hemagglutinin. Glycans are of great importance for the medical field: for example, it is possible to detect Alzheimer's disease at an early stage by examining the state of the glycans attached to the surface of blood cells.

Figure 2 Functions of glycans



- Regulation of gene functions
- Regulation of antibody functions
- Differentiation of blood type
- Decoration of proteins
- Protein quality control
- Binding to extracellular proteins
- Binding to vibrio choleria and E.coli O-157
- Binding to influenza viruses and bacteria
- Determination of cancer metastasis
- Molecules that bind to glycans are used in cancer diagnosis
- Treatment of cancer and Alzheimer's disease

Source: Produced by MGSSI using the diagram from Sharon and Lis *Glycobiology* (2004) 14:53R..

[5] For detailed information on glycans see *Essentials of Glycobiology, 2nd Edition,* Maruzen, and *Tosa Seibutsugaku: Seimei Gensho to Tosa Joho (Glycan Biology: Biological Roles of Glycan Chains)*, The University of Nagoya Press. The full text of *Essentials of Glycobiology, 3rd Edition* is available online at https://www.ncbi.nlm.nih.gov/books/NBK310274/

LECTINS AND EXOSOMES

What are lectins?

Lectin is a generic term for proteins that possess the property of binding to glycans on the surface of cells. Lectins are widely present in the fluids, cells, organs, etc. of viruses, microorganisms, plants, animals, and humans. The first report of a lectin is said to have occurred in 1860 with the observation of a substance (a lectin) in rattlesnake venom that causes hemagglutination (the clumping of a large quantity of red blood cells)[6]. (It is commonly believed that lectins were first discovered in 1888 in studies conducted by the Estonian microbiologist Peter Hermann Stillmark.) Lectins gained a certain amount of recognition in 1978 when an exiled Bulgarian writer was assassinated with an umbrella containing ricin. Ricin is one type of lectin, and even a tiny amount of this substance is capable of killing a person[7].

Functions and types of lectins

Due to the manner of their discovery, lectins were not used in the medical field because of a long-held misunderstanding that all lectins have a toxic effect of causing hemagglutination. However, as research into lectins progressed, it became apparent that, conversely, this property of hemagglutination can be used for purposes such as determining blood groups in humans, and cell staining to assist in pathological diagnosis. In addition, lectins identify old proteins and transport them to intracellular lysosomes (responsible for waste disposal) for degradation, and they have also been found to function like immune cells by patrolling the blood vessels to detect and neutralize harmful bacteria.

While ordinary proteins stick rigidly to performing a single given function, lectins are referred to as "**protein mavericks**"[8] due to their unique property of adapting to circumstances accompanying changes in an organism's environment. The main types of lectins are shown in Figure 3.

Figure 3 Main types of lectins

Lectin type	Description
Galectin	The only cytoplasmic lectin. It is involved in the transmission of information between cells.
Selectin (C-type lectin)	Involved in leukocyte infiltration in the interaction between leukocytes and endothelial cells during inflammation
Siglec (I-type lectin)	Exists on the surface of immune cells and recognizes glycans of antigens such as bacteria
R-type lectin	Present in a wide range of organisms. Ricin is also an R-type lectin.(*1)
L-type lectin	Undertakes functions of sorting and transportation of intracellular glycoproteins, and biological defense functions
P-type lectin	Transports enzymes(*2) in intracellular lysosomes
Calnexin/Calreticulin	Lectins involved in protein folding
Annexin	Present in almost all cells, it passes through the cell membrane to the cell's exterior.
Legume lectin	The largest family of plant lectins, it is involved in the sorting and transportation of proteins.

*1: A lectin termed seviL that binds to tumor cells in the human autoimmune disease Guillain Barré syndrome has been found in Japanese mussels. https://doi.org/10.1111/febs.15154
*2: Lysosomal enzymes include a wide range of enzymes, including hydrolases, and enzymes that break down proteins and nucleic acids.

Source: Produced by MGSSI based on various information sources

[6] Hideyo Noguchi was one of the researchers who conducted detailed studies on hemagglutination reaction in snake venom along with Simon Flexner. He also discovered a lectin called Limulin in the hemolymph of the horseshoe crab. Limulin was the first discovery of a lectin derived from animals.

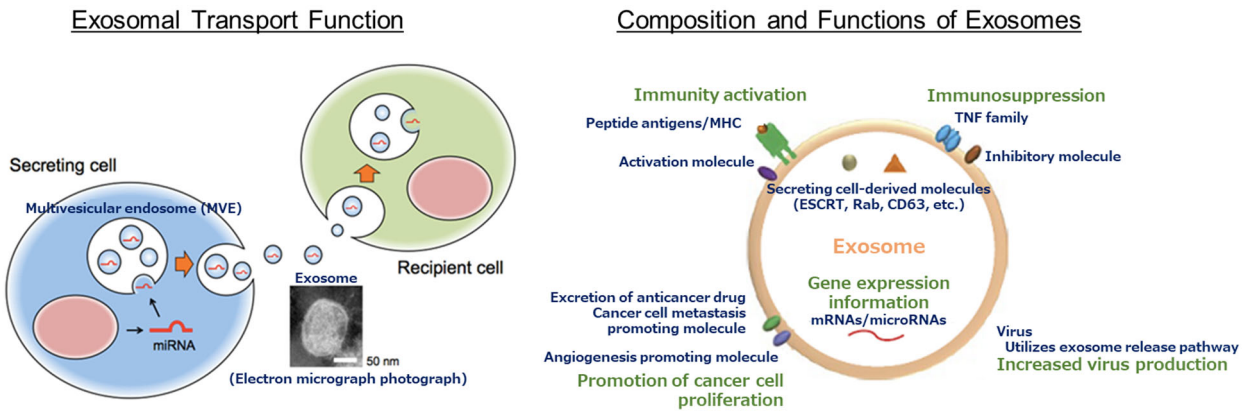
[7] The lethal dose is 150 µg for a body weight of 50 kg. Ricin is a highly toxic substance 500 to 1,000 times more potent than potassium cyanide, and is considered to be the most likely substance to be used for bioterrorism. The Committee for State Security (KGB) of the former Soviet Union is said to have made heavy use of ricin for political assassinations. In Japan, ricin is designated as a "specific chemical" under the Act on the Prohibition of Chemical Weapons and the Regulation of Specific Chemicals, and its manufacture, possession, and use are prohibited.

[8] The expression "protein maverick" (*tanpakushitsu no itanji* in Japanese) was quoted from *Oshaberina To, Daisan no Seimei Ango* written by Kenichi Kasai (Iwanami Shoten) p.52.

What are exosomes?

Cells are constantly taking in “sacs” containing external substances, and at the same time, filling “sacs” with internal substances and releasing them to the outside. In particular, sacs with a diameter of 50-150 nm (nanometer: one billionth of a meter) are called “exosomes”[9] (Fig. 4). It was initially thought that the exosomes discharged from cells simply contained cellular “waste”. However, in 2007, a Swedish scientist who was analyzing the content of exosomes discovered the presence of nucleic acids such as DNA and RNA. In addition to DNA, exosomes also contain **messenger RNA** (mRNA)[10] and **micro-RNA** (miRNA)[11], which indicates that nucleic acids may be delivered to other cells by exosomes, and research in this area has been recently accelerating. The 2013 Nobel Prize in Physiology or Medicine was awarded for the achievement of elucidating the manner in which exosomes are released by cells and transported and delivered to other cells.

Figure 4 Overview of exosomes



Source: (Left) Department of Molecular Oncology, Institute of Medical Science, Tokyo Medical University
http://team.tokyo-med.ac.jp/ims_onc/research/report01.html
(Right) FUJIFILM Wako Pure Chemical Corporation https://labchem-wako.fujifilm.com/jp/siyaku-blog/011004.html

Exosomes are released from almost all cells and can be easily extracted from body fluids such as blood, urine, saliva, and breast milk. These exosomes contain many biological substances such as proteins and lipids in addition to DNA and RNA, and by examining the miRNA, which is one of the substances they contain, it is possible to determine what kind of cancer is present in a patient[12]. The test method whereby exosomes obtained from body fluids are examined for the presence of cancer is known as a **liquid biopsy**[13]. Exosomes also function as carriers that transport biological substances to other cells. For example, exosomes that are released by cancer cells are loaded with substances that replicate the cancer cells. Since cancer cells proliferate, it is known that the release of exosomes loaded with cancerous material spreads the cancer to other organs. The next section describes a DDS (Drug Delivery System) that delivers drugs to the required location using this ability of exosomes to carry materials from cell to cell.

[9] Discovered in 1983, they were given the name exosome in 1987.
[10] Messenger RNA is RNA that carries a copy of the genetic information of DNA and delivers it to a protein’s biosynthesis mechanism.
[11] Studies have shown that micro-RNA is RNA that does not carry genetic information and that it is involved in life phenomena such as the development, differentiation, proliferation, and death of cells. miRNA is attracting particular attention because it regulates gene expression.
[12] Details concerning miRNA that has been confirmed to be present in the exosomes in the body fluid of cancer patients can be found at https://www.gelifesciences.co.jp/newsletter/201707_exosome.html.
[13] In addition to exosomes, liquid biopsies used for cancer diagnosis also target circulating tumor cells and circulating tumor DNA.

LECTINS AND EXOSOMES ARE REVOLUTIONIZING MEDICINE AND DRUG DISCOVERY

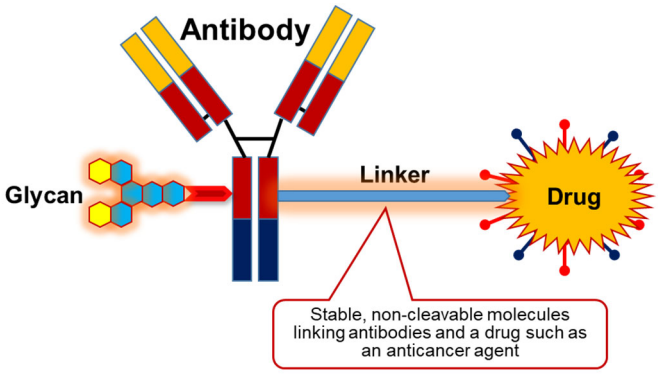
This section describes (1) **antibody-drug conjugates** and (2) **lectin-drug conjugates**, currently being studied as DDS, before describing (3) **lectin-exosome-drug conjugates**, which are expected to be the next-generation DDS, and **lectin-artificial exosome-drug conjugates**, which is the developed form of the (3) above.

(1) Antibody-drug conjugates (for reliable delivery of drugs)

When a foreign body such as a pathogenic bacterium (an antigen) enters the human body, the body produces an antibody which binds to the foreign body to neutralize it. This process is called an **antigen-antibody reaction** or an **immune reaction**. An **antibody drug** is a therapeutic agent that utilizes this antigen-antibody reaction mechanism. For example, in the case of the antibody drug **Kymriah**[14] used for the treatment of leukemia, first the patient's immune cells (T-cells) are collected from the patient's blood, the immune cells are genetically modified in order to enhance their ability to attack cancer cells, and the enhanced immune cells are returned to the patient to attack and kill the cancer cells. This therapeutic method is called **gene modified T-cell therapy using chimeric antigen receptor T-cells** (generally referred to as **CAR T-cell therapy**). While Kymriah is expected to be effective against cancer, it can cause serious side effects[15], and it is a demanding therapy for the patient.

Research in the field of antibody drugs is focused on **antibody-drug conjugates** (ADC), a DDS that is based on a new concept. ADCs consist of an antibody to which a drug is bound (Fig. 5), and the drug is released after being taken up by the cell together with the antibody.

Figure 5 Schematic of an antibody-drug conjugate



Source: Produced by MGSSI based on various information sources

Antibody-drug conjugates are effective for treating intractable cancer and recurrent cancer, and they have been the subject of over 50 clinical trials conducted overseas. However, it has been pointed out that the search has been carried out for almost all proteins that serve as antigens for antibody drugs and antibody-drug conjugates, and it is difficult to envisage further significant progress. In the medical and drug discovery fields, rather than antibody drugs and antibody-drug conjugates, a completely different approach that will lead to the emergence of drugs that are safe, inexpensive, and patient-friendly is in demand.

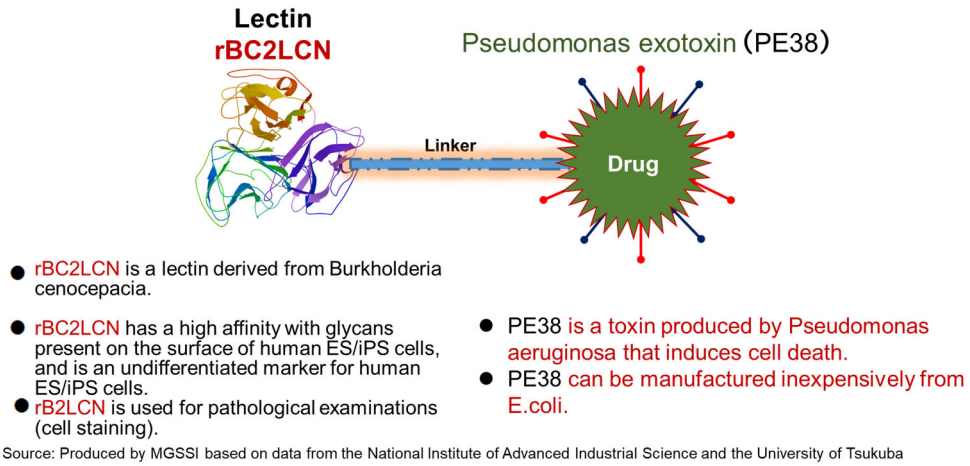
(2) Lectin-drug conjugates (for reliable delivery of large doses of drugs)

One notable candidate in the field of drug discovery that is not based on the immune response is lectins. The National Institute of Advanced Industrial Science and the University of Tsukuba have discovered a lectin named **rBC2LC-N** that does not demonstrate hemagglutination activity. The researchers have investigated the use of rBC2LC as a carrier for delivering drugs, and have actually developed a DDS termed a **lectin-drug conjugate**

[14] Kymriah is a drug developed by Novartis Pharma for the treatment of leukemia. It costs ¥33,493,407 per patient.
[15] Although antibody drugs such as Kymriah target specific proteins on the surface of cancer cells, those proteins also exist on many normal cells, and those normal cells are attacked as well as the cancer cells.

(LDC) in which rBC2LC-N is fused with an anticancer drug (Pseudomonas exotoxin (PE38)) (Fig. 6), which they administered to mice with pancreatic cancer.

Figure. 6 Schematic of a lectin-drug conjugate administered for pancreatic cancer

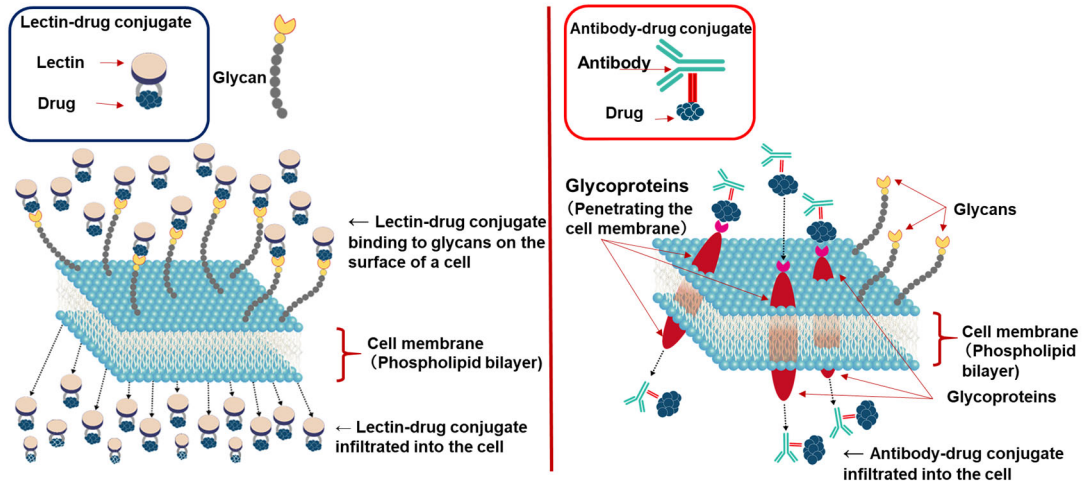


Source: Produced by MGSSI based on data from the National Institute of Advanced Industrial Science and the University of Tsukuba

The result of administration of this lectin-drug conjugate is reported to have been favorable and to have demonstrated an anticancer effect 1,000 times more powerful than that of existing antibody drugs[16]. Antibody drugs make use of the "antigen-antibody reaction", in which each antigen reacts with a single antibody[17]. However, there are only a small number of antigens on the surface of a cell, and so even when antibodies are delivered to the cell, the amount of drug that enters the cell is tiny, and the drug needs to be administered repeatedly to achieve a good therapeutic effect[18]. The image on the right in Figure 7 below shows the mechanism of an antibody-drug conjugate, and it can be seen that the pharmacological effect is weak even when the drug is taken up by the cell.

The left-hand image in Figure 7 shows a large number of lectin-drug conjugates binding to a large quantity of glycans (several hundreds to several thousands) flourishing on the surface of a cell, thereby reliably delivering the drug to the diseased cell. For example, if the dose of drug delivered to a cell by an antibody-drug conjugate

Figure 7 Schematic of a lectin-drug conjugate and an antibody-drug conjugate



Source: Produced by MGSSI based on data from the National Institute of Advanced Industrial Science and the University of Tsukuba

[16] Website of the National Institute of Advanced Industrial Science: https://www.aist.go.jp/aist_j/press_release/pr2017/pr20170926/pr20170926.html

[17] In the case of some antibodies, there are also multispecific antigens that have multiple antigen binding sites. For details see *Nature* Volume 580 15 April 2020 "Multispecific drugs herald a new era of biopharmaceutical innovation". This article gives a panoramic overview of the history of biopharmaceuticals up to the present day. https://doi.org/10.1038/s41586-020-2168-1

[18] The immune checkpoint inhibitor Opdivo introduced in footnote 1 is administered 26 times a year.

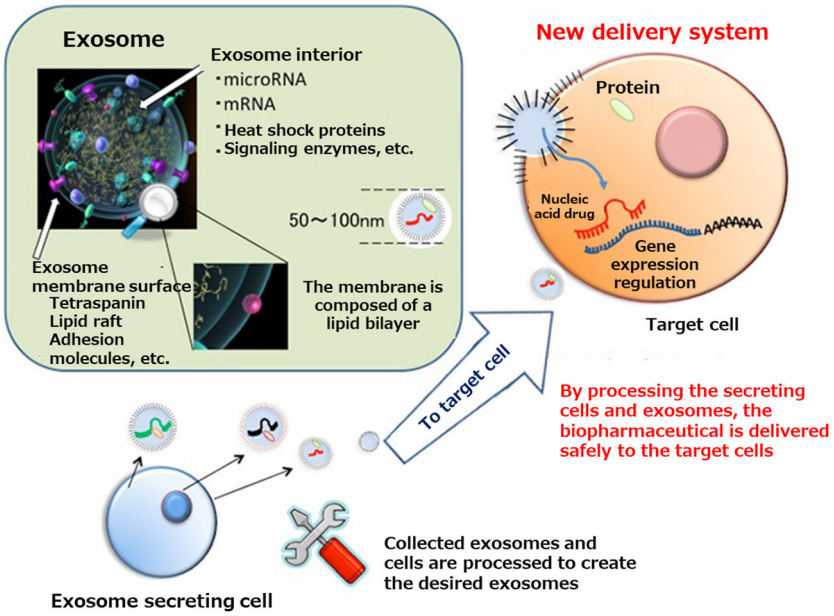
is taken as 1, a lectin-drug conjugate can deliver a dose of 1,000 and achieve a far higher pharmacological effect. Investigations conducted by the University of Tsukuba into the binding effect of lectin rBC2LC-N using the tissue of 69 patients who had undergone surgery for pancreatic cancer found that it bound strongly to the cancerous tissue of almost all the subjects.

Pancreatic cancer is one of the most intractable cancers, with a five-year survival rate of 10% (the average five-year survival rate for all cancers is approximately 60%). A group headed by Professor Tatsuya Oda at the University of Tsukuba is currently conducting a pre-clinical study of the treatment of pancreatic cancer with a lectin-drug conjugate[19]. The study is funded by a grant-in-aid for scientific research, and this therapy is expected to contribute significantly to the treatment of pancreatic cancer and other diseases.

(3) Lectin-exosome-drug conjugates (for safe, reliable delivery of large doses of drugs)

Section (2) above described lectin-drug conjugates that utilize lectins' function as a carrier for delivering drugs. Since exosomes also possess the function of transporting substances to distant cells, research is underway into a DDS capable of delivering anticancer drugs and **next-generation therapeutic drugs** (**small molecule drugs**[20], **nucleic acid drugs**[21]) contained within exosomes into diseased cells. In particular, exosomes have the property of encapsulating drugs and protecting them from the external environment, which is an excellent property for use in a DSS. For example, in the case of small molecule drugs and nucleic acid drugs, there is a drawback that when the drug is administered directly into the body as it is, there is a significant risk that it will be broken down by proteolytic enzymes or nucleolytic enzymes present in body fluid, making it difficult to achieve a pharmacological effect. In short, a valuable drug needs to be wrapped in a "sac", i.e., an exosome, and moved safely through the body to reach the targeted destination (Fig. 8).

Figure 8 Schematic of a DDS using exosomes



Source: Basic Science and Platform Technology Program for Innovative Biological Medicine
https://www.amed.go.jp/program/list/06/01/i-biomed/subject/2014/13/index.html

[19] Three grant-in-aid for scientific research R&D projects are currently in progress: (1) Development of an innovative cancer treatment using a lectin conjugate to target cancer cell surface glycans (2018-2022, ¥44 million); (2) Development of a lectin drug targeting cancer cell glycans as a post-antibody drug: Preclinical study of a pancreatic cancer therapy using an rBC2 lectin-drug conjugate (2018-2020, ¥160 million); (3) Lectin imaging: Innovative cancer diagnostic imaging using sugar-binding protein (2019-2023, ¥26 million). https://research-er.jp/researchers/view/114983

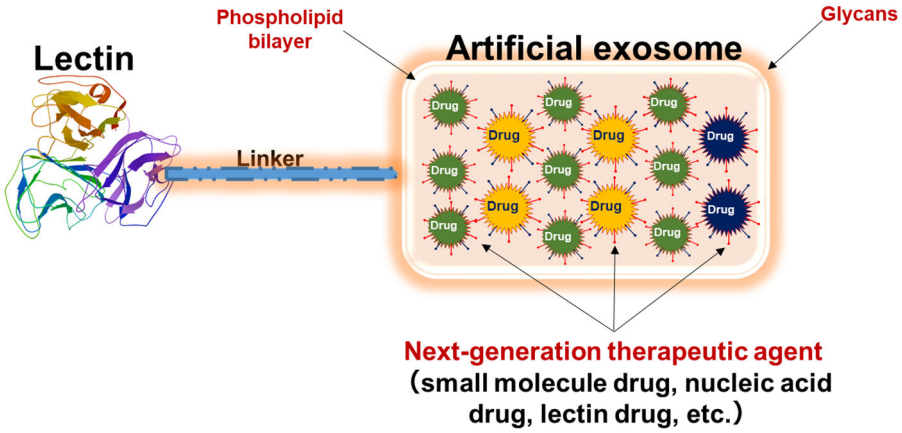
[20] As the name suggests, small molecule therapeutics are drugs with small molecules. Because the small size of the molecules allows the drug to penetrate into every corner of a cell, the therapeutic effect is expected to be enhanced.

[21] Drugs using nucleic acid (DNA) are expected to have the potential to treat diseases that are difficult to treat with small molecule therapeutics and antibody drugs.

It is believed that a **lectin-exosome-drug conjugate** utilizing lectins that can reach diseased cells reliably and in large quantities, along with a next-generation therapeutic drug contained in exosomes, will be an effective next-generation DDS. For example, when pancreatic cancer has been diagnosed by means of a liquid biopsy, a lectin conjugate for pancreatic cancer is created. This raises the prospect that by attaching an anticancer drug (Pseudomonas exotoxin (PE38)) to this conjugate, as performed by the National Institute of Advanced Industrial Science and Technology, or creating a **lectin-exosome-drug conjugate** by combining exosomes containing a next-generation therapeutic drug, such as a small molecule drug or a nucleic acid drug, and then administering it, it will be possible to reliably deliver the drug to diseased cells and lead to a complete cure.

However, since exosomes secreted in the body are minute in size, this method has the drawback that the amount of a drug they can hold is inevitably extremely small. For this reason, a means of increasing the carried amount of the drug and enhancing the pharmacological effect is required. In this respect, it is believed that it will be possible to create artificial exosomes leveraging synthetic biology[22], and combining them with lectins to deliver large doses of drug to diseased cells. In the future, **lectin-artificial exosome-drug conjugates** combining lectins and artificial exosomes, capable of carrying multiple drugs in large doses (Fig. 9), may bring about drugs with dramatically higher therapeutic effects.

Figure 9 Lectin-artificial exosome-drug conjugate



Source: Produced by MGSSI based on various information sources

FUTURE PROSPECTS

Except for being used for a DDS, drugs making use of the various functions of lectins are currently being developed for other applications. For example, the lectin known as **galectin** is being clinically applied for its effect in delaying the progression of liver disease. In addition**, selectin** is undergoing a clinical trial as a treatment for vascular occlusion, while **siglec** is known to be effective against autoimmune and inflammatory diseases. There are also drugs using lectins for diseases that do not respond to existing drugs, such as a synthase inhibitor that prevents hypertrophy of the liver and spleen (Fig. 10). Recent findings have revealed that some lectins function as **immune checkpoint molecules**[23], suggesting the possibility of a new cancer immunotherapy. Lectins are attracting attention as a new area in drug discovery because they can be produced in large quantities by microorganisms.

[22] Synthetic biology is an area of research that seeks to elucidate the basic principles of life phenomena by "creating" the functions of cells and other biological entities based upon the knowledge acquired to date in biology and the life sciences through engineering techniques.

[23] Immune checkpoint molecules are a group of molecules that suppress the autoimmune response in order to maintain immune homeostasis, and also suppress excessive immune reaction. While, essentially, they exist to suppress excessive activation of T-cells and to prevent attacking themselves, in the carcinogenic process they are used by cancer cells to avoid attack from the immune system and to proliferate.

Figure 10 Lectin drugs

Glycan drugs	Overview	Realization time frame
Galectin inhibitors	Expected to be used in drug development because galectins are involved in various life phenomena.	TD139 is in clinical trials in the UK as an inhaled medication for idiopathic pulmonary fibrosis. Within 10 years.
Selectin inhibitors	Selectin is effective in the treatment of vascular occlusion in sickle cell disease, acute myelocytic leukemia, multiple myeloma, etc.	Currently in clinical trials as a vascular occlusion agent for sickle cell disease. Chemokine receptor inhibitor. Within 5 years.
Siglec control agents	Expected to be used in drugs for autoimmune diseases and inflammatory diseases because siglecs have a signaling function and are expressed in immune cells.	It is necessary to develop compounds that are easy to synthesize and possess excellent active properties and pharmacokinetic effects. Within 5 years.
Synthase inhibitors	Effective for hypertrophy of the liver and spleen caused by excessive accumulation of specific glycans, such as Gaucher disease, and for diseases presenting central nervous system symptoms.	Practical application of the synthase inhibitor Eliglustat for Gaucher disease. Other synthase inhibitors within 5 years.

Source: Produced by MGSSI based on various information sources

Other than their role in effectively delivering biopharmaceuticals, such as antibody drugs, small molecule drugs, and nucleic acid drugs currently being developed, to diseased cells, exosomes are also likely to be widely used in the diagnosis of various diseases in the future. Already promising in areas such as cancer diagnosis, respiratory diseases such as bronchial asthma, kidney and liver diseases, and neurological diseases such as Alzheimer's disease, exosomes have the potential to cover almost all the major human diseases. Also, since exosomes are released by cells infected with the HIV virus, hepatitis C virus, TB, and other diseases, they are also effective in detecting viral and bacterial infections.

Chronic obstructive pulmonary disease (COPD) has been indicated as an aggravating factor for the novel coronavirus (COVID-19) and it is feared that it will rise in the rankings to the third leading cause of death in the world from 2020. This pathological condition has been revealed by research into exosomes. The global market for exosome diagnostics and therapies is forecast to grow to US$186.2 million by 2023[24], and they are expected to change the shape of the medical and drug discovery fields and disease control in the future.

CONCLUSION

An initiative termed "**Choosing Wisely**[25]" that seeks to allocate medical resources to worthwhile medical treatment is spreading in the US. In Japan, too, a system called "Formulary" that predesignates the most effective and economical drug regimen for patients is spreading, and it is believed that, in the future, greater importance will be placed on transitioning from treatment with expensive drugs with strong side effects that place a burden on patients to "value-based medicine" that respects the wishes of patients and prioritizes patient value. Lectins and exosomes will be the powerful tools for realizing this transition through the use of DDSs, lectin drugs, and exosome diagnostics technology.

It may be that "**ubiquitous healthcare**", which treats disease by extracting the maximum benefit from the functions of biological substances that ubiquitously exist throughout the human body, such as glycans, lectins, and exosomes, will become the mainstream of healthcare in the future.

[24] BCC Research https://www.bccresearch.com/market-research/biotechnology/exosome-diagnostics-and-therapeutics-global-markets-report.html

[25] An international campaign aimed at encouraging the selection of medical treatments (testing, treatment, procedures) that are supported by scientific evidence, that are truly necessary for the patient, and that have few side effects, through dialogue between healthcare professionals and patients. https://choosingwisely.jp/service/