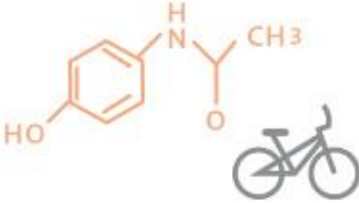

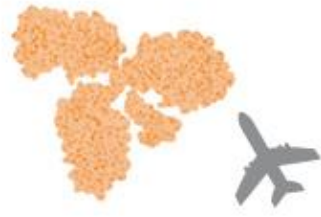

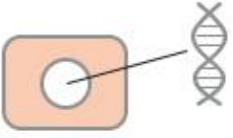


What are Biologics?

Differences with Conventional Drugs


Biologics vs. Small molecules

Other than differing greatly in molecular size, **small molecules** are produced by chemical synthesis while **biologics** are created using biotechnology and referencing biomolecules (enzymes, hormones, antibodies, etc.) in the human body.

	Conventional drugs (low-molecular weight compounds)	Biologics (e.g. recombinant proteins)	
Size (molecular weight)	100 and above	About 10,000 and above (hormones, etc.)	About 100,000 and above (antibodies)
Size and complexity (visual representation)			
Manufacturing method (visual representation)	Chemical synthesis 	Cultured microorganisms and cells Microorganisms and cells  Genes of antibodies, etc.	

Based on "Current State of Biosimilars" by the Ministry of Health, Labour and Welfare (July 23, 2015)

High Expectations for Biologics



Hope for effectively treating previously hard-to-treat diseases

Advances in biopharmaceuticals have made it possible to treat a wide range of diseases. Since biopharmaceuticals are made by leveraging the functions of substances produced in the human body, there is a high expectation that they will effectively treat diseases for which there are no drugs available or no conventional treatments with high therapeutic effect. *

*"What Are Biopharmaceuticals?"

http://www.ebe-biopharma.org/index.php?option=com_content&task=view&id=26&Itemid=102

Examples of biologics and its application

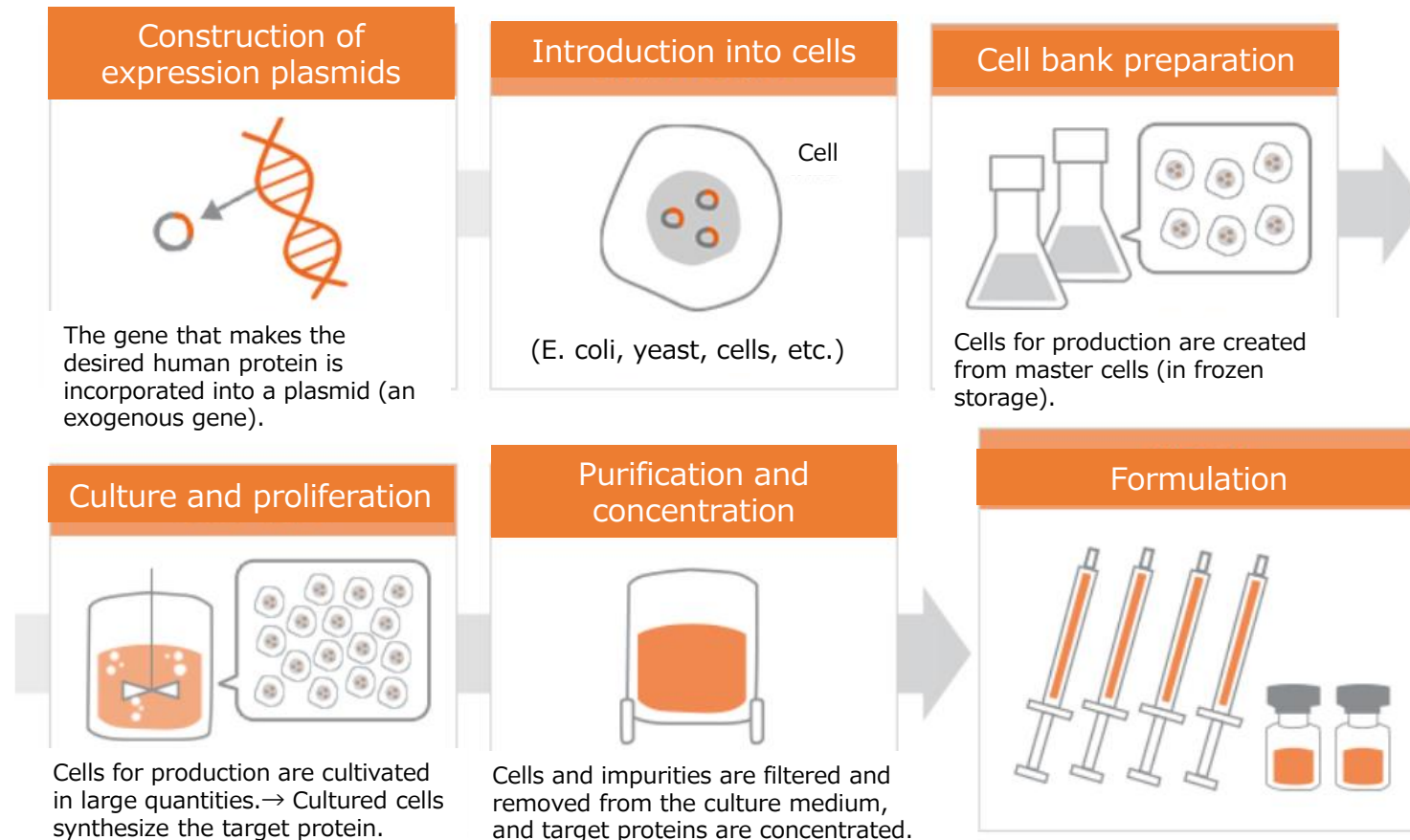
Active ingredient	Major indications
Adalimumab	Rheumatoid arthritis
Rituximab	Non-Hodgkin's lymphoma
Trastuzumab	Breast cancer
Nivolumab	Malignant melanoma
Interferon	Type C hepatitis
Pegfilgrastim	Neutropenia
Ustekinumab	Psoriasis vulgaris
Ranibizumab	Age-related macular degeneration
Dupilumab	Atopic dermatitis
Insulin	Diabetes
Ocrelizumab	Multiple sclerosis

Source: Compiled by Kirin based on Evaluate Pharma

Basic Biopharmaceutical Manufacturing Process

A Typical Utilization of Gene Engineering in Biotechnology

→ Conventional drugs are mainly small molecules produced by chemical synthesis. In contrast, **biologics** are produced from **animal cells and other microorganisms** using **biotechnology** such as genetic recombination.



Based on "Current State of Biosimilars" by the Ministry of Health, Labour and Welfare (July 23, 2015)

Biopharmaceutical Manufacturing Process using Cell Culture Bioreactors & Fermentation

Biopharmaceutical fermentation of cell culture shares the **same technology** with health food/alcohol fermentation in terms of **maximizing the production of target enzymes, proteins, or metabolites.**

Bioreactor
Kyowa Kirin Takasaki Plant
(Gunma Prefecture)



- **Active ingredients of biopharmaceuticals are produced from cell culture in the bioreactor.**

Lactobacilli culture tank
iMUSE Health Science Factory
(Saitama Prefecture)



- **Lactobacilli are grown** from sugar and other raw materials.

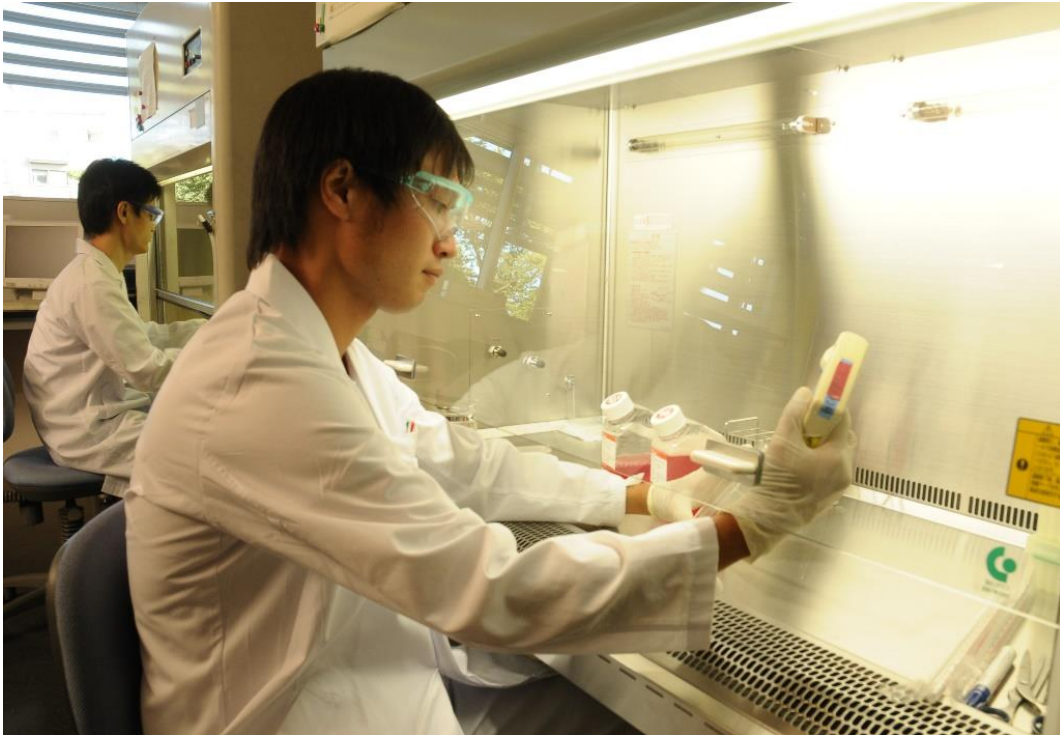
Beer fermentation tanks
Pilot Plant
(Kanagawa Prefecture)



- Sugar is metabolized by **brewer's yeast** to produce **ethyl alcohol** and **carbon dioxide.**

Birth of Biopharmaceuticals at Kirin Group

From Biotechnology Research to Biopharmaceuticals



The Development & Research Committee was established in December 1972 to explore the use of the **biotechnologies** accumulated within the company to enter new business fields and thus promote business diversification.

In the mid-1970s, the company worked on immunostimulatory anticancer drugs using polysaccharides (KS extracts) derived from Shiitake mushrooms. This effort was eventually discontinued due to a lack of reproducible data meeting the evaluation criteria for immunostimulants set by the Ministry of Health and Welfare (now the Ministry of Health, Labour and Welfare). Nevertheless, the company's acquisition of basic working knowledge for **drug** development, strengthening of its R&D capabilities, the development of internal human resources, and the formation of human networks, as well as biotechnology for producing foods and beer during this period all contributed greatly to its entry into the **pharmaceutical** business.

In 1982, the Research & Development Department was established, and the company **initiated the commercialization of biopharmaceuticals** by applying the biotechnology it had developed through its extensive experience.

What are Pharmaceutical Antibodies?

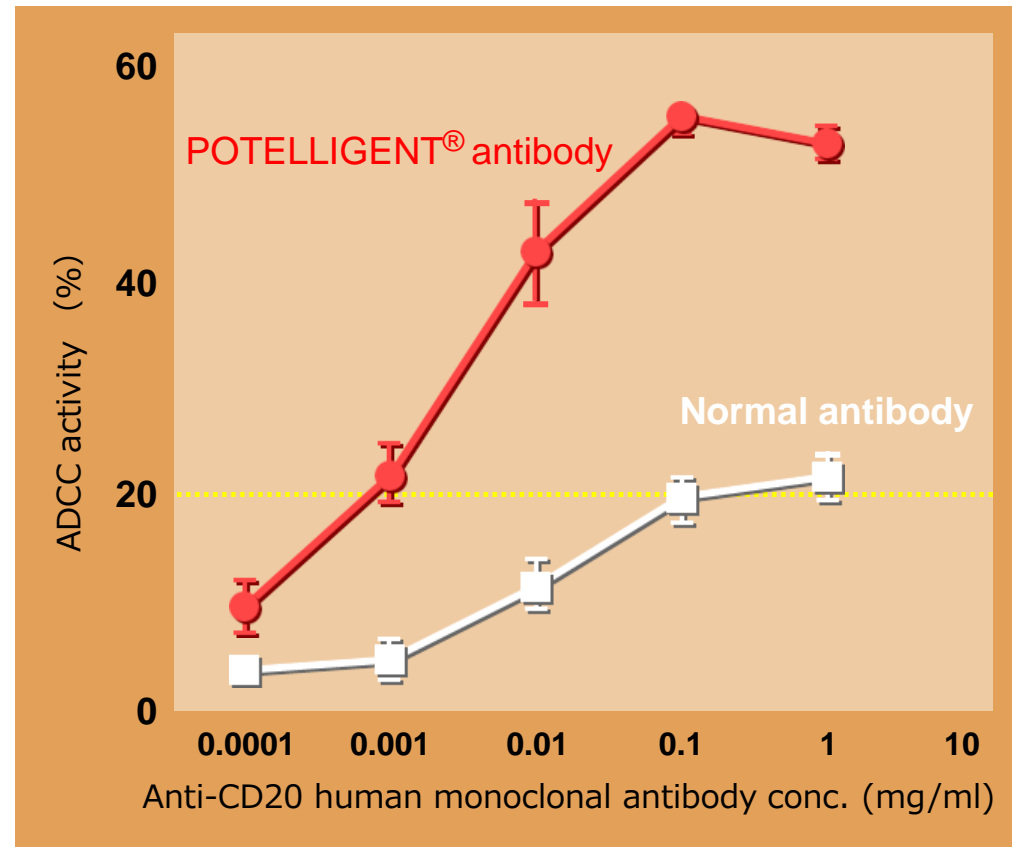
A Ray of Hope

Pharmaceutical antibodies are biologics based on antibodies, which are proteins that play a role in the body's immune system and characterized by their ability to act on specific targets. With this feature, they are expected to be highly effective drugs with fewer side effects.

The Kirin Group's **pharmaceuticals business (Kyowa Kirin)** possesses **proprietary antibody-based technologies**, such as **Potelligent** and **Complegent**, which enhance the antibody activity, and **Human Antibody Production Technology**, which enables the efficient production of fully human antibodies.



Antibodies:
Key components of pharmaceutical antibody



Shinkawa et al., J. Biol. Chem, 278(5) 3466-3473, 2003

Kyowa Kirin's pipeline

Biopharmaceutical (non-antibody) pipeline

As of June 30, 2020

