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)	HO NY CH3			
Manufacturing method (visual representation)	Chemical synthesis	Cultured microorganisms and cells Microorganisms and cells		

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

## Biopharmaceuticals Contributing to the Future of Medicine High Expectations for Biologics

### <u>Hope for effectively treating</u> <u>previously hard-to-treat diseases</u>

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 ingredie	nt 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

# Pipeline of antibody drugs

#### As of June 30, 2020

Development code	Targot diseases	Country or region		Development stage				
(generic name)	larget diseases			Phase I	Phase II	Phase III	Application	
KW-0761 (Mogamulizumab)	Fungoid granuloma and Sezary syndrome	Australia		$\rightarrow$				
	Adult T-cell leukemia-lymphoma	United States, Europe and others			$\rangle$			
	HTLV-1-associated myelopathy	Japan						
	Psoriasis	Malaysia and Macau						
KHK4827 (Brodalumab)	Axial spondyloarthritis	Japan, Taiwan						
	Systemic sclerosis	Japan						
	Palmoplantaris pustulosis	Japan						
KHK4083	Atopic dermatitis	Japan, North America, Europe						
ASKP1240 (bleselumab)	Recurrence of Focal Segmental Glomerulosclerosis (FSGS) in de novo kidney transplant recipients	USA			>			
KHK6640	Alzheimer's disease	Europe and Japan						
KRN23 (Burosumab)	X-linked hypophosphatemia	Kuwait, Saudi Arabia, Bahrain, Taiwan, China and Singapore						
	Adult X-linked hypophosphatemia	Europe				<u> </u>		
	FGF23-related hypophosphatemic rickets and osteomalacia	Korea		_				
	C	Oncology	Immune and Allergic Diseases	Centr syste	al nervous m	Other are	eas	

### Kyowa Kirin's pipeline

# Biopharmaceutical (non-antibody) pipeline

As of June 30, 2020

Development code		Country or region of development		Development stage			
(generic name)	larget diseases			Phase I	Phase II	Phase III	Application
KW-3357 (antithrombin gamma)	Preeclampsia	Japan			$\rangle$		
	Disseminated intravascular coagulation, congenital antithrombin deficiency	Europe		-			
KRN125 (pegfilgrastim)	Mobilization of hematopoietic stem cells into peripheral blood	Japan			>		
	Automated infusion device for the prevention of febrile neutropenia in patients receiving cancer chemotherapy	Japan			>	>	
AMG531 (romiplostim)	Aplastic anemia who have had an inadequate response to conventional therapy	Taiwan			$\geq$		<u> </u>
		Korea		_	>		
	Aplastic anemia who were previously untreated with immunosuppressive therapy	Japan, Korea and Taiwan		_			
	Idiopathic (immune) thrombocytopenic purpura	China					
		Nephrology	Immune and Allergic Diseases	Onco	logy	Other are	eas