



R&D at the Kirin Group

～ Development of Technologies to Expand Our Business Domains
and Solve Social Issues ～

October 6, 2020

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Director of the Board
Senior Executive Officer
Kirin Holdings Company, Limited

Expanding the Kirin Group's technological capabilities and business domains

Biotechnology evolved from beer brewing

Living organism-based manufacturing interests in which are growing

Technical capabilities to solve social issues

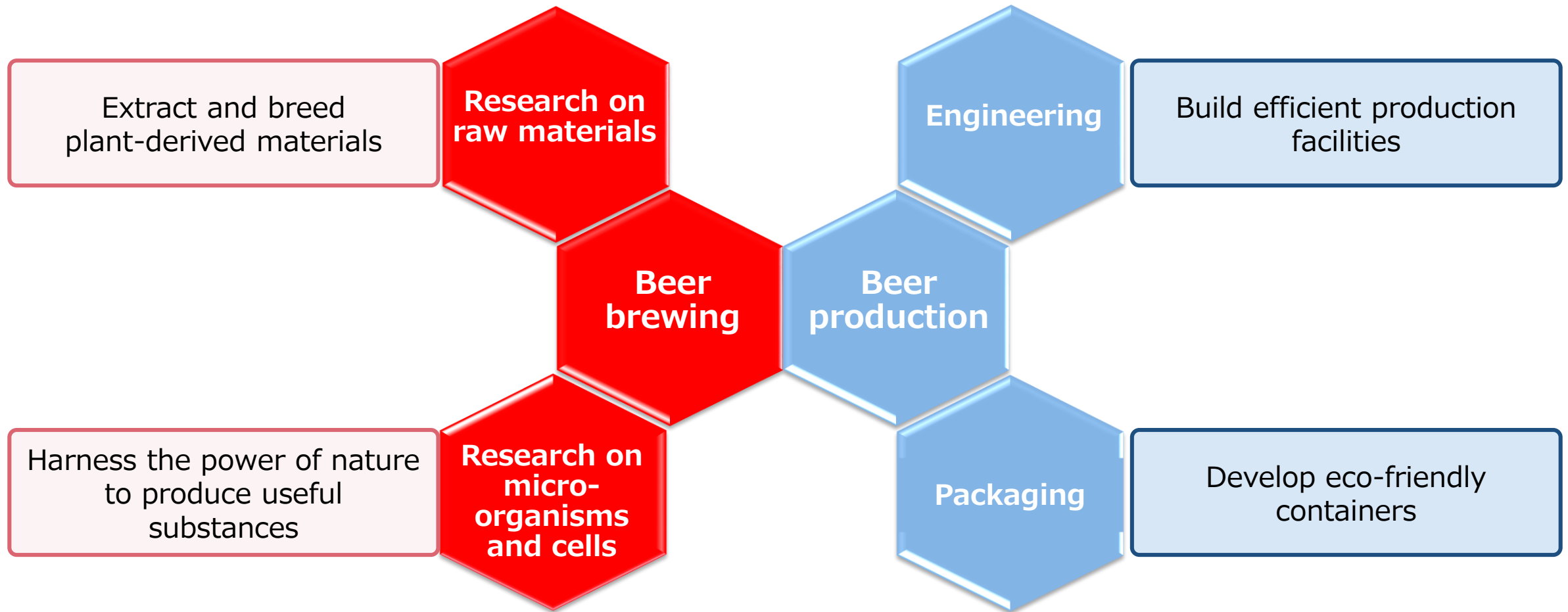
Social issues and problems in the health & well-being domain

Vision and three key domains based on technological capabilities

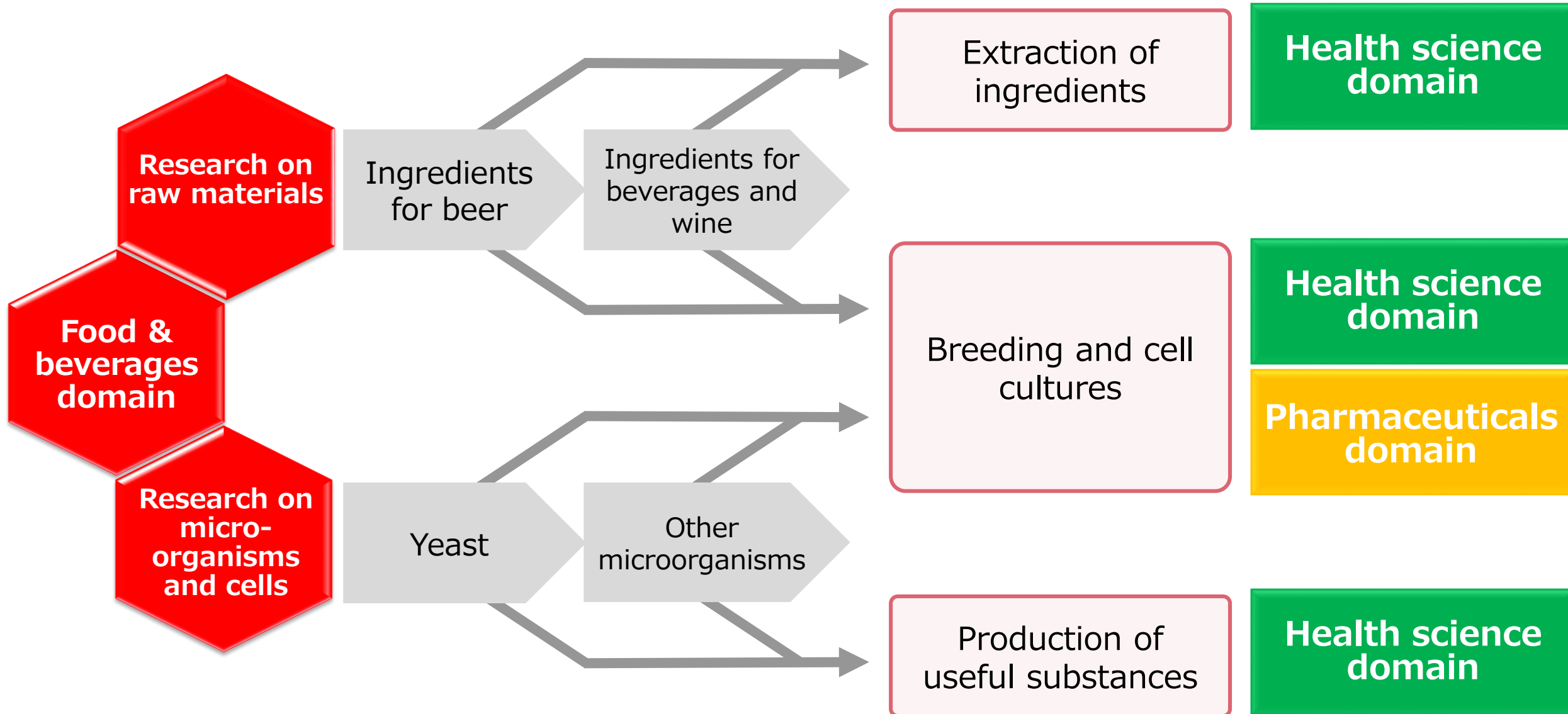
Strengthening our research system and open innovation

Expanding the Kirin Group's technological capabilities and business domains

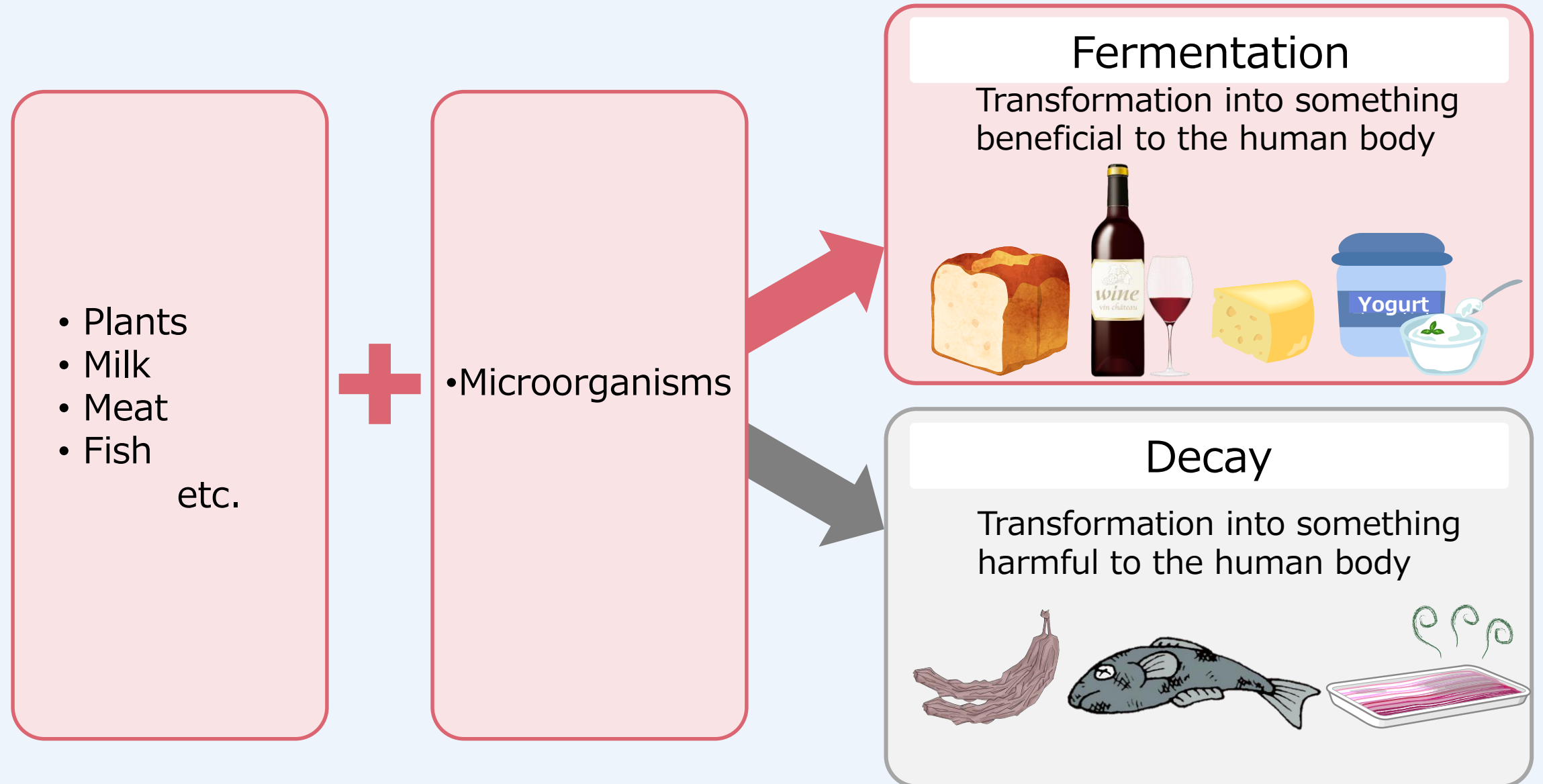
1. Technologies of the Kirin Group



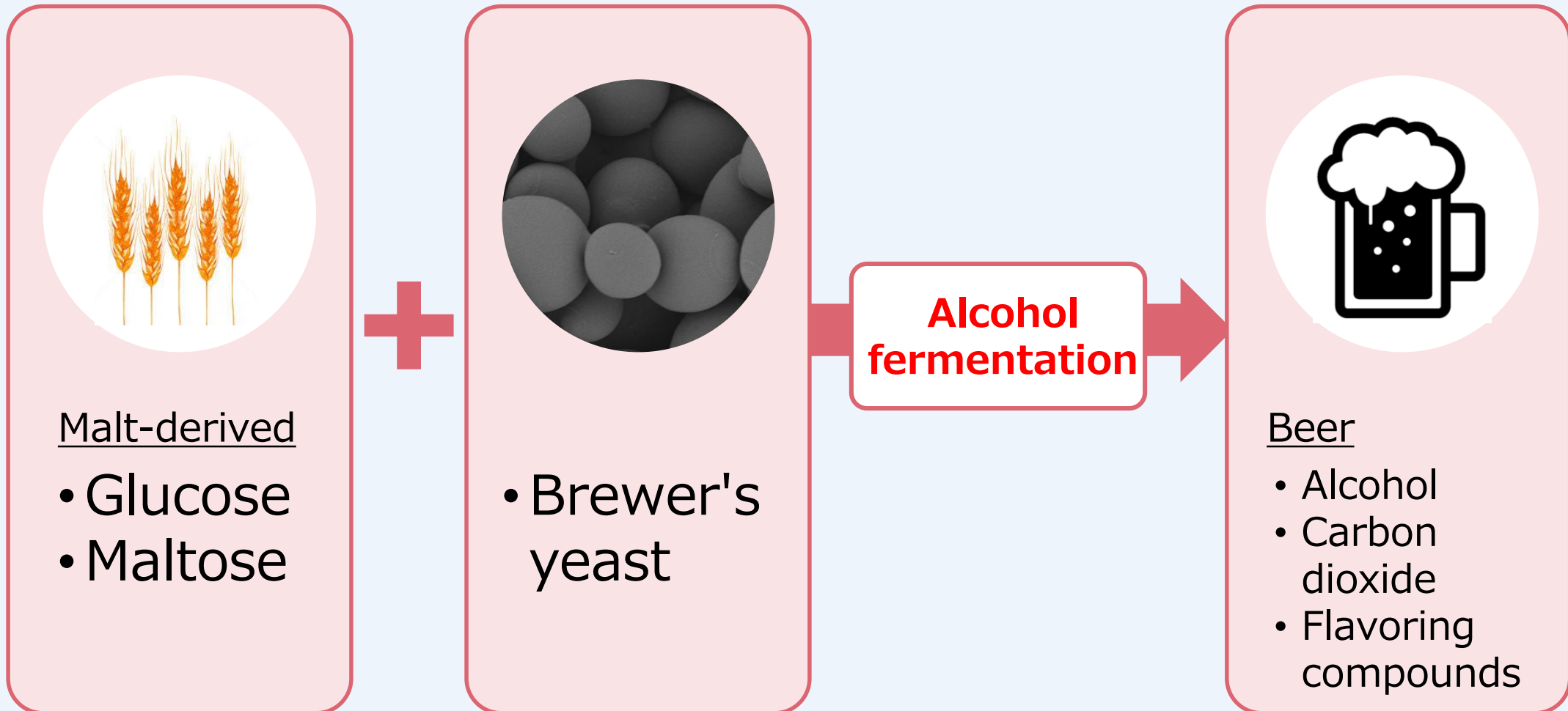
2. Fermentation and biotechnology



3. What is fermentation?

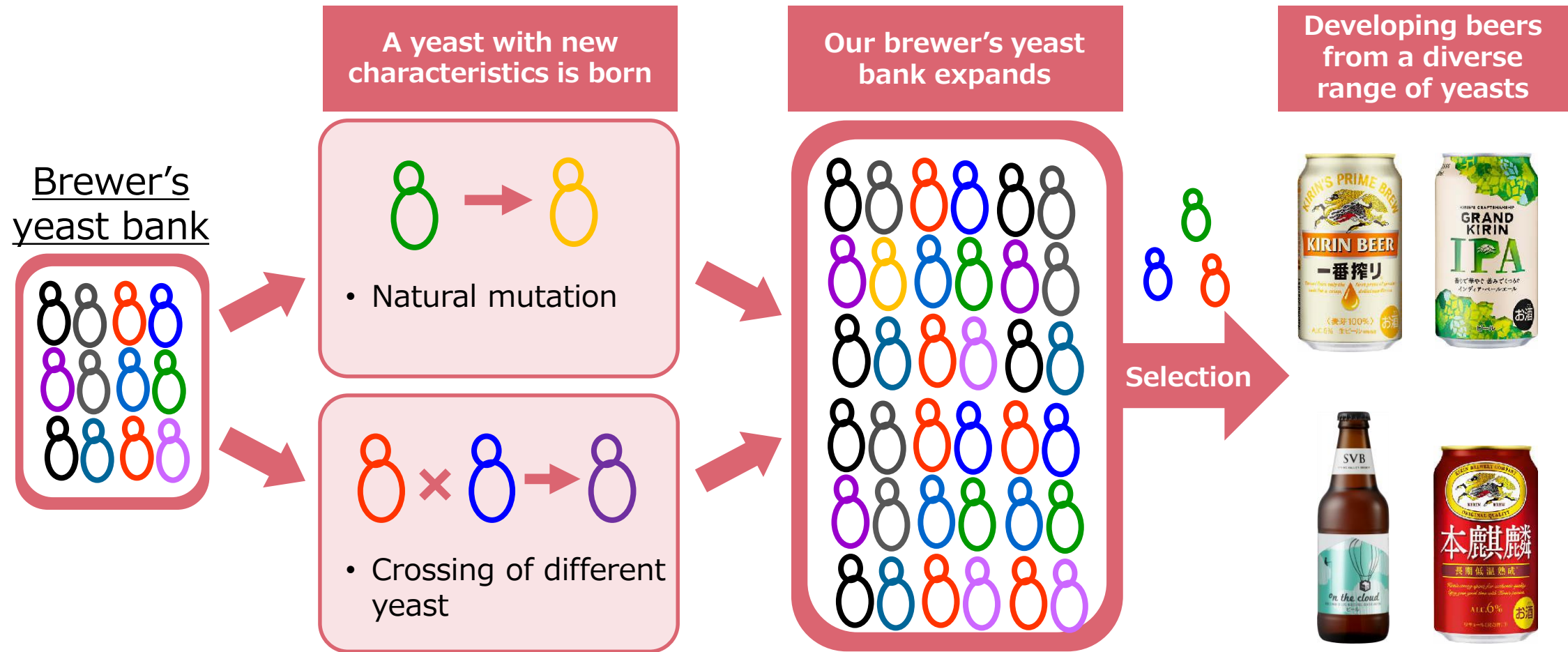


4. Fermentation in beer brewing

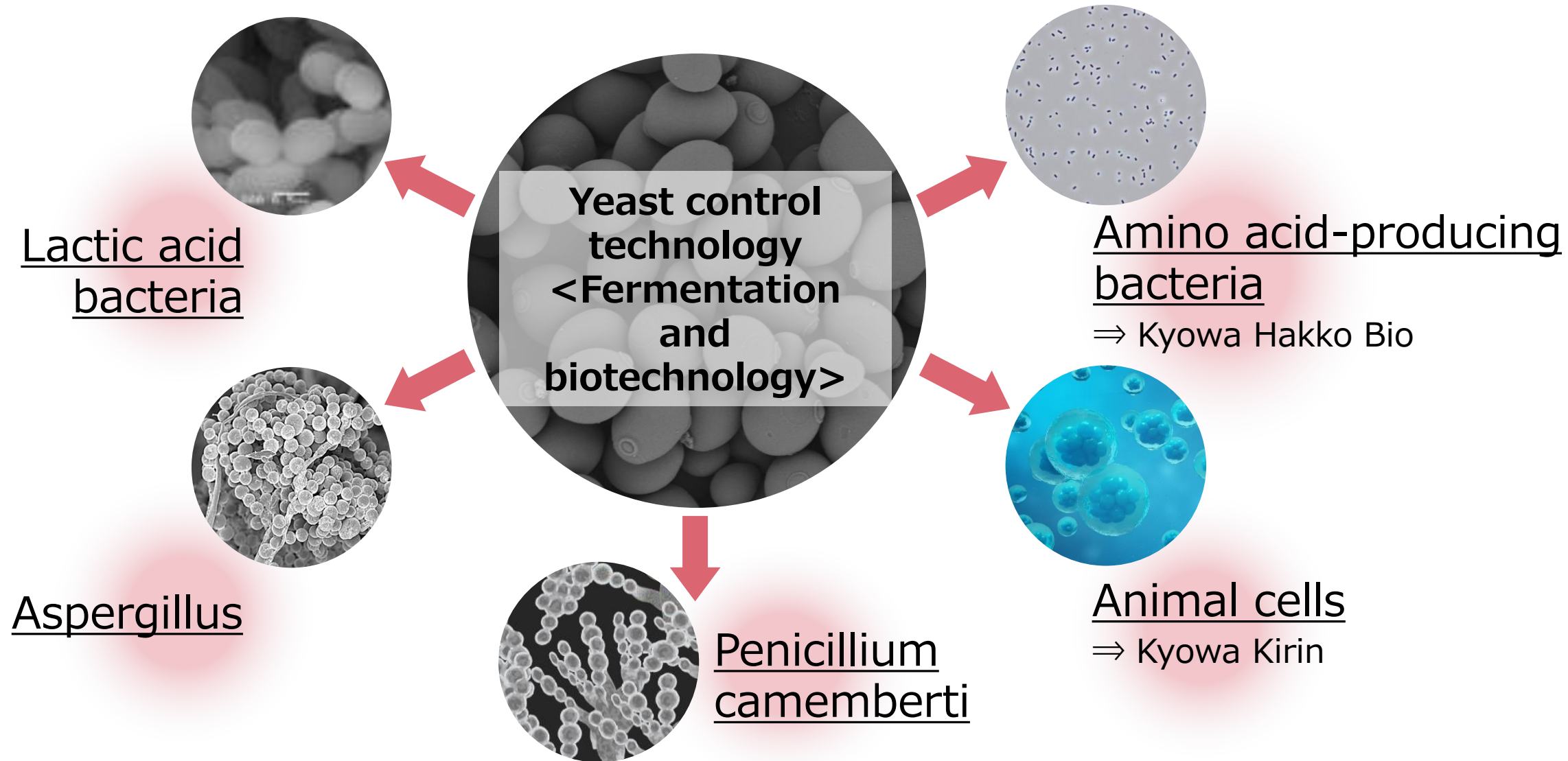


5. Research on yeast in Kirin Beer

- Our technologies have been producing a wide variety of yeast
- We have approximately 1,000 types of beer yeast



6. Extending the technology from yeast to other microorganisms



7. Discovering useful substances that contribute to health through the power of microorganisms

Beneficial bacteria

- Yeast fungus
- *Lactococcus lactis* strain Plasma
- KW lactobacilli
- Yeast plant
- *Penicillium camemberti*
- Amino acid-producing bacteria
- *Coryneform* group

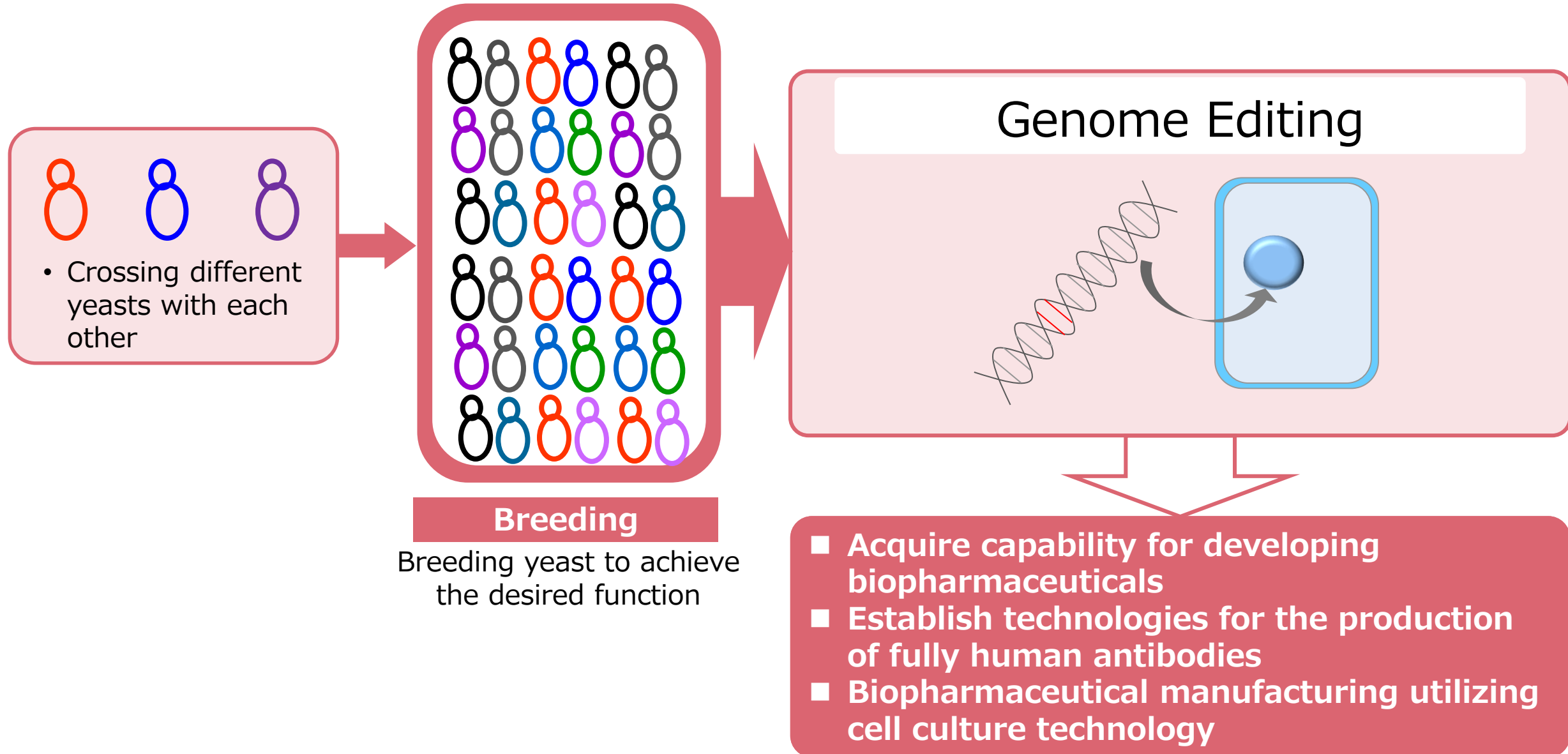
Useful substances

- Citicoline
- Beta-lactolin
- Matured hop extract
- Glutamine
- Citrulline
- Arginine
- Ornithine
- FAD^{*}
- ATP^{**}
- Human milk oligosaccharides
- Koji (malted rice) sterols
- Black tea extract
- Resveratrol


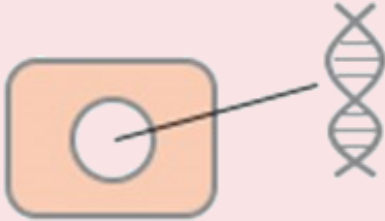
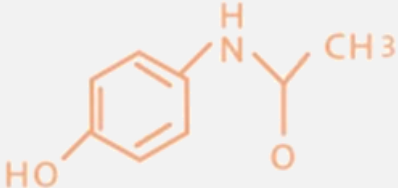

* FAD (flavin adenine dinucleotide): coenzyme-type vitamin B2 preparation

** ATP(Adenosine 5'-Triphosphate Disodium Hydrate): metabolic stimulant

8. From breeding to gene design technology



9. Biopharmaceuticals

	Conventional pharmaceuticals (small molecule drugs)	Biopharmaceuticals (e.g. recombinant proteins)
Manufacturing method (visual representation)	Chemical synthesis 	Microorganisms and cells 
Size and complexity (visual representation)		
Size (molecular weight)	100 or greater	About 10,000 or greater (hormones, etc.) About 100,000 or greater (antibodies)

10. Development of our first pharmaceutical

Development of erythropoietin (EPO) at Kirin

1980s

- Hypothesis formulated in the 1980s

A hormone involved in hematopoiesis (EPO) is secreted by the kidney; if kidney function declines, EPO will no longer be produced and anemia may develop as a result

- Started researching EPO in-house to prove this hypothesis
Reduced production of EPO was confirmed as a cause of anemia

- Partnership with Amgen started in 1984 (Kirin-Amgen Co., Ltd. established)
Research and development on erythropoietin continued

- Human erythropoietin is successfully isolated and cloned in 1985*

1990s

- Human erythropoietin (recombinant) is approved and launched in Japan in 1990
Our erythropoietin product, which has equivalent structural characteristics, immunological and biological properties to those of human erythropoietin (derived from urine), is now on the market

* Lin FK, Suggs S, Lin CH, et al. Cloning and expression of the human erythropoietin gene. Proc Natl Acad Sci USA. 1985; 82: 7580-7584.

11. Expanding our business domains through fermentation and biotechnology

Joy brings us together
KIRIN

Food domain

Kirin Brewery

Beer

Expanding the scope of
our business through
fermentation technology

Seasoning
(amino acids)

Pharmaceuticals

Alcoholic
beverages

Non-alcoholic
beverages

Health-promoting
substances

Health-promoting
substances

 **KIRIN**


KYOWA

Pharmaceuticals
domain

**Kyowa Hakko
Kogyo**

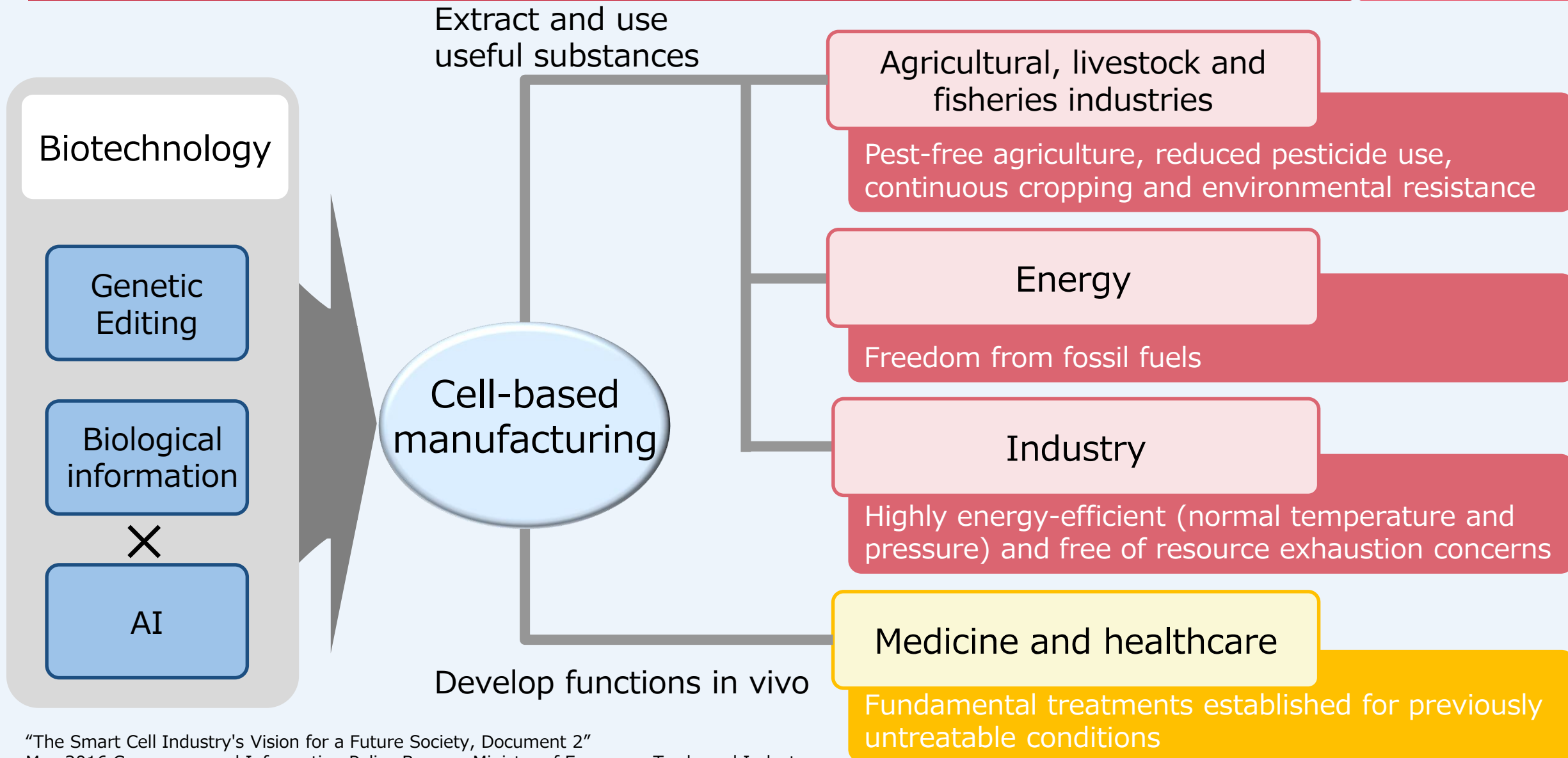
Pharmaceuticals
biochemicals

- Acquire capability for developing biopharmaceuticals
- Establish technologies for the production of fully human antibodies
- Biopharmaceutical manufacturing utilizing cell culture technology

- Enhance ability to create biopharmaceuticals
- Establish Potelligent technology

 **KYOWA KIRIN**

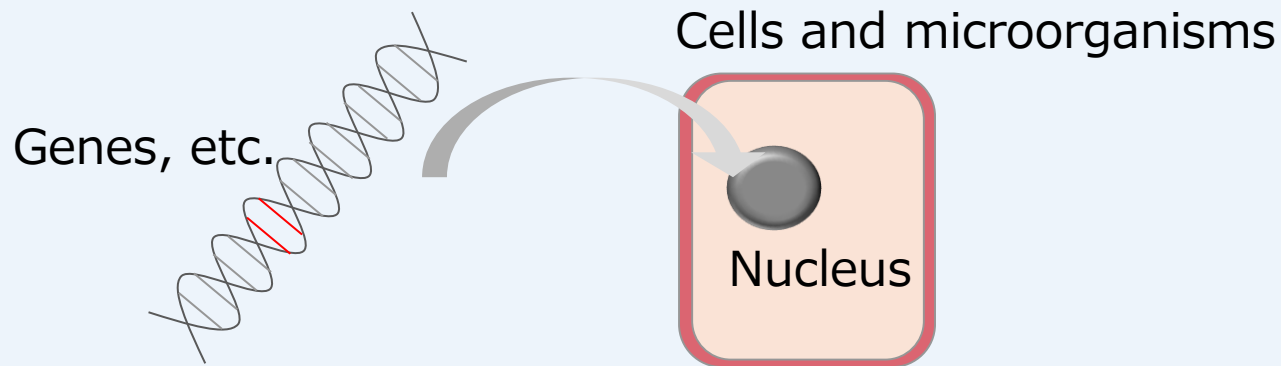
12. Growing hopes for biotechnology



"The Smart Cell Industry's Vision for a Future Society, Document 2"

May 2016 Commerce and Information Policy Bureau, Ministry of Economy, Trade and Industry

13. Living organism-based manufacturing



Substances that can be synthesized by living organisms

Food

Bio
pharma
ceuticals

Proteins

Sugars

High-
performance
chemicals

Low
molecular-
weight
chemicals

Low-
molecular
weight
pharmace
uticals

Metal

Substances that can be synthesized by the chemical industry

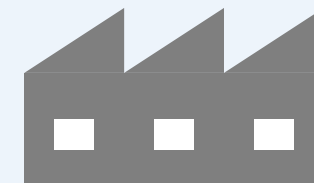
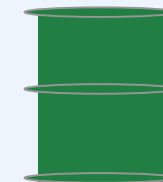


KYOWA KIRIN



Kirin's business domain:
Substances that can be synthesized only by living organisms

Oil

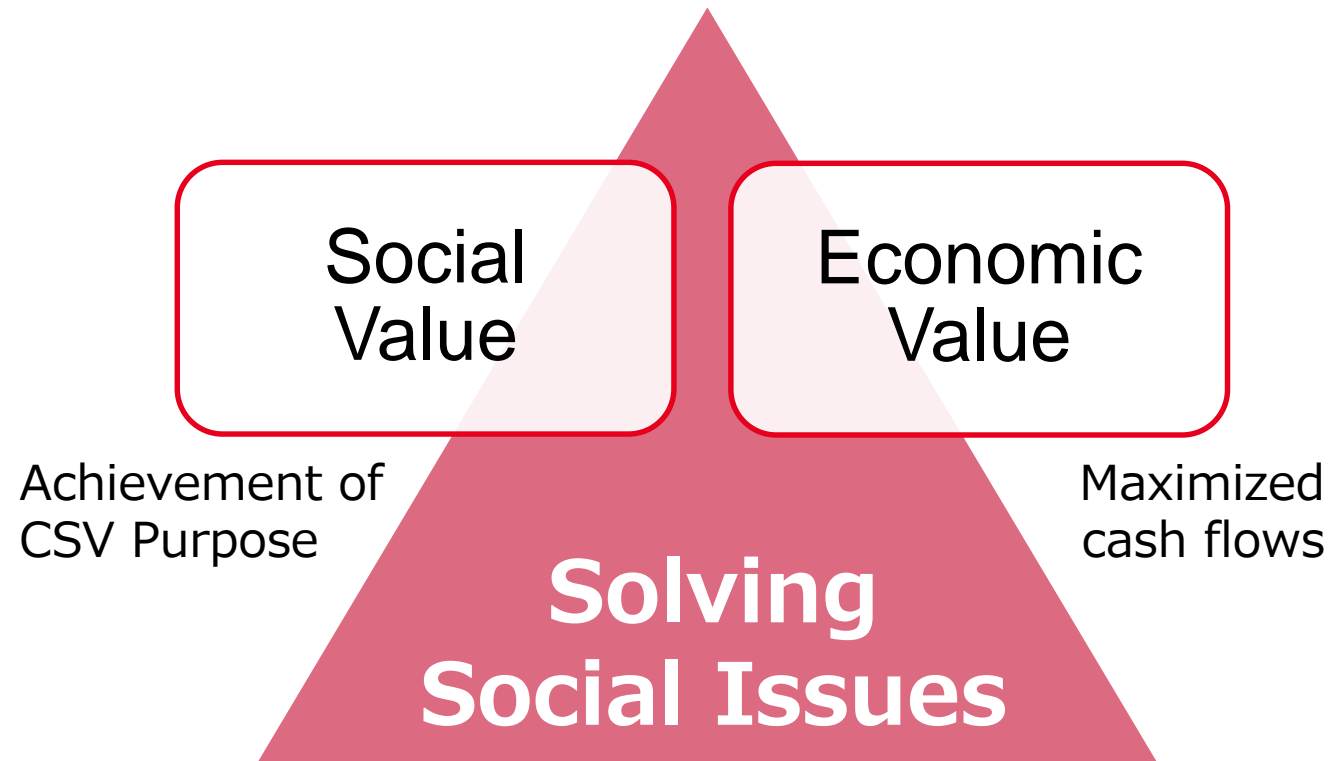


Technical capabilities to solve social issues

14. Aim for growth through Creating Shared Value (CSV)

**Become a leading global CSV company and
aim to maximize Social and Economic Value**

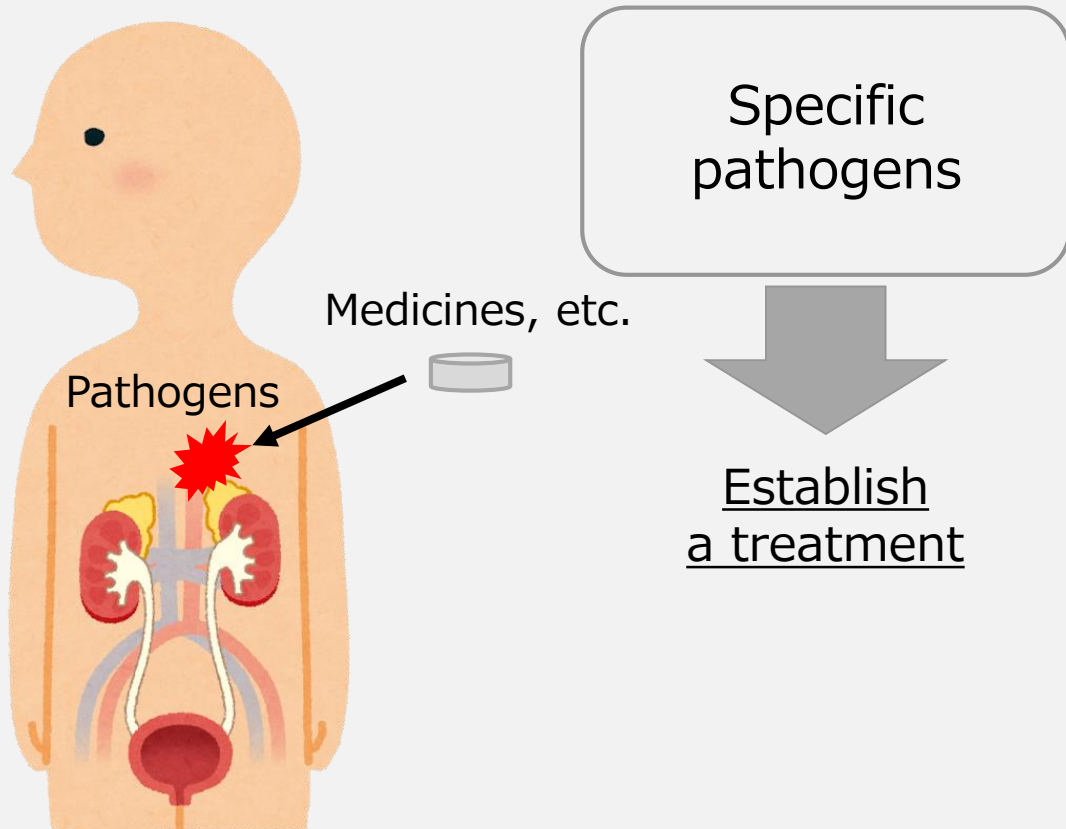
Sustainable Growth



15. Social issues related to health and well-being

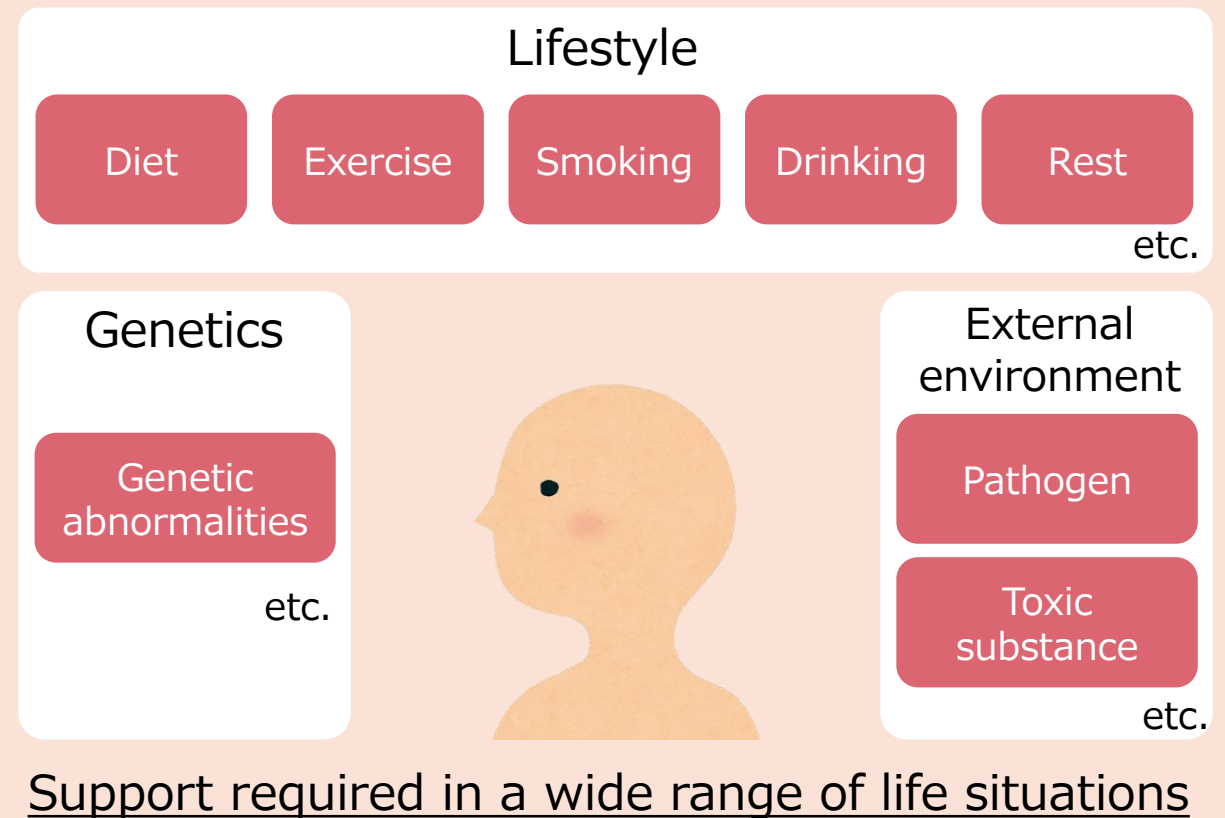
All patients share the same pathogenesis
(single factor)

Approach to pathogens



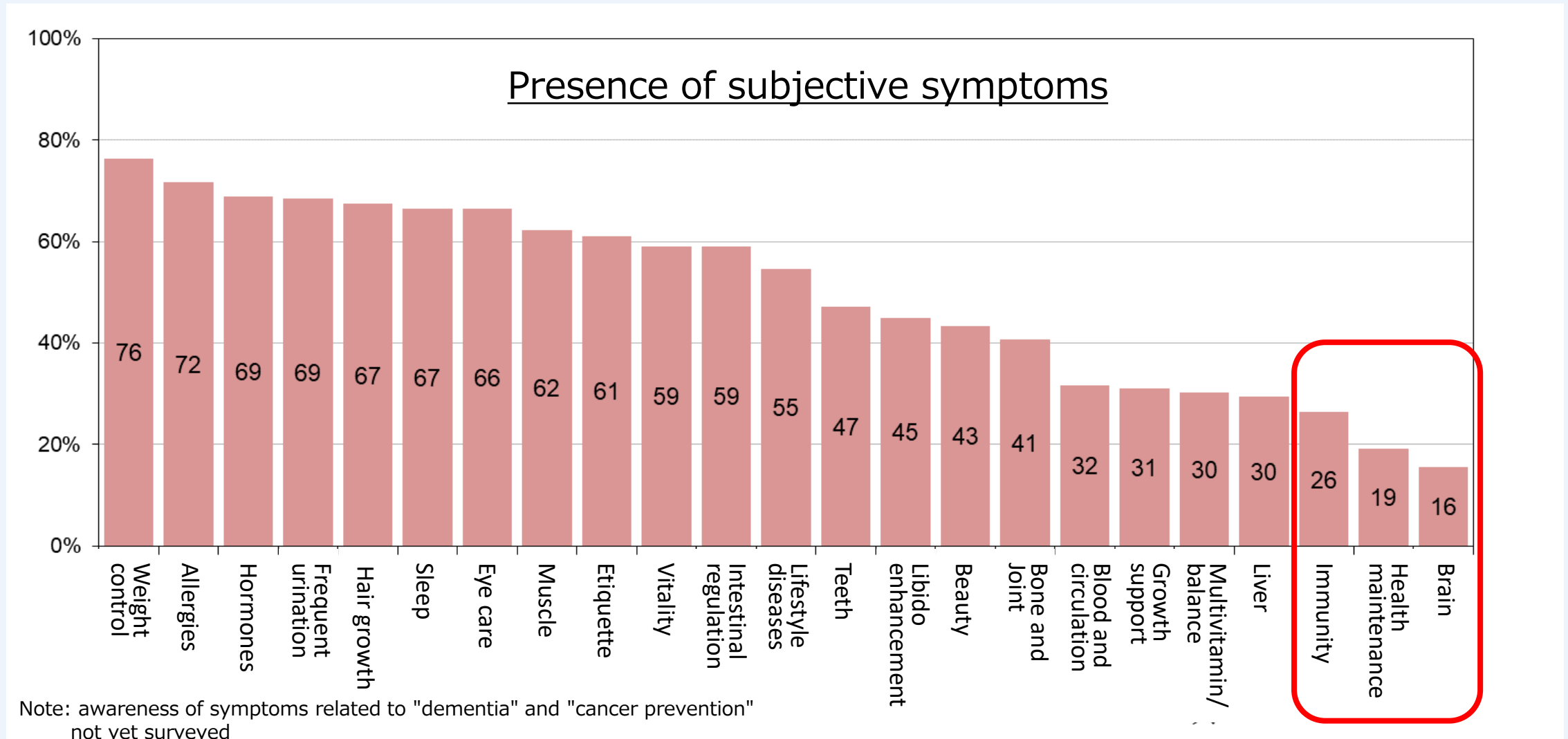
Diseases with different pathogens in different patients
(multifactorial)

Individualized approach

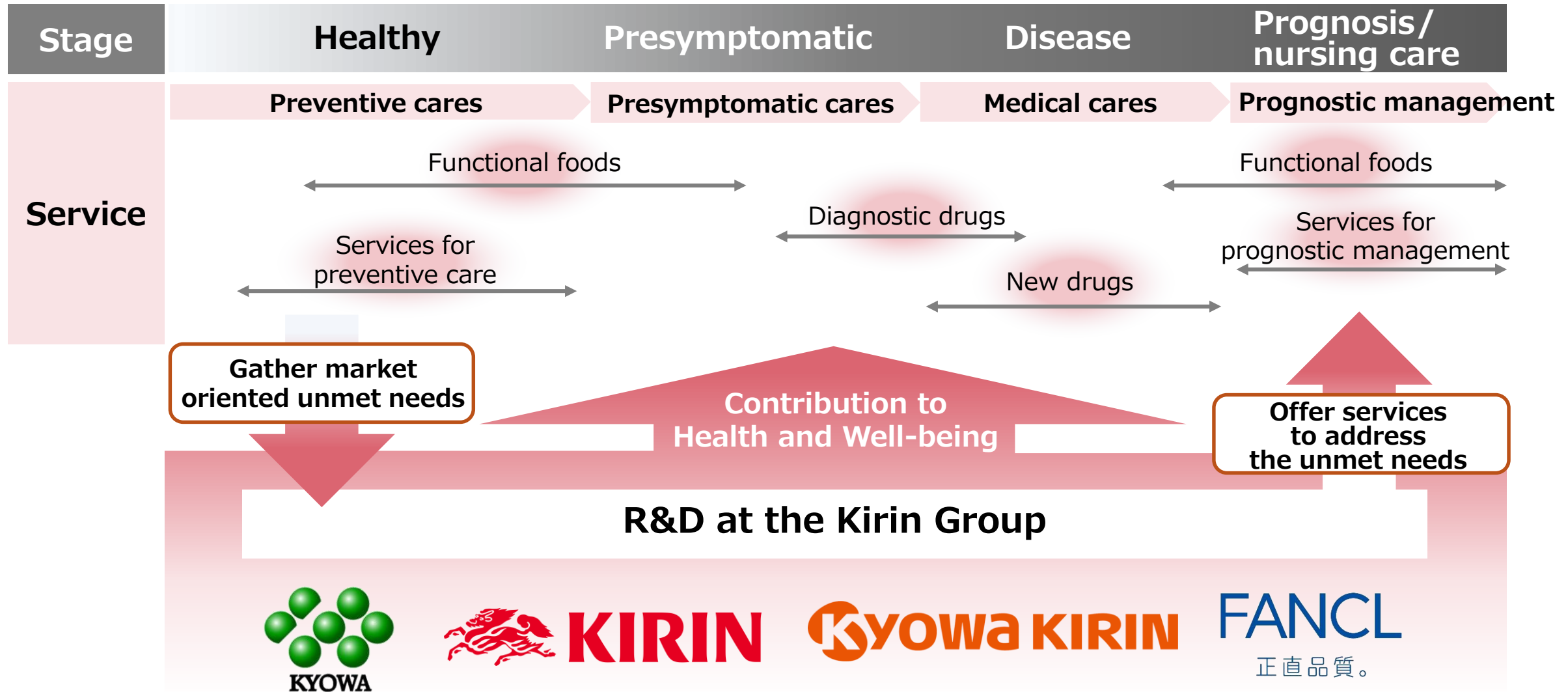


16. Delay in taking action due to minor nature of subjective symptoms

■ Challenges in having needs become tangible

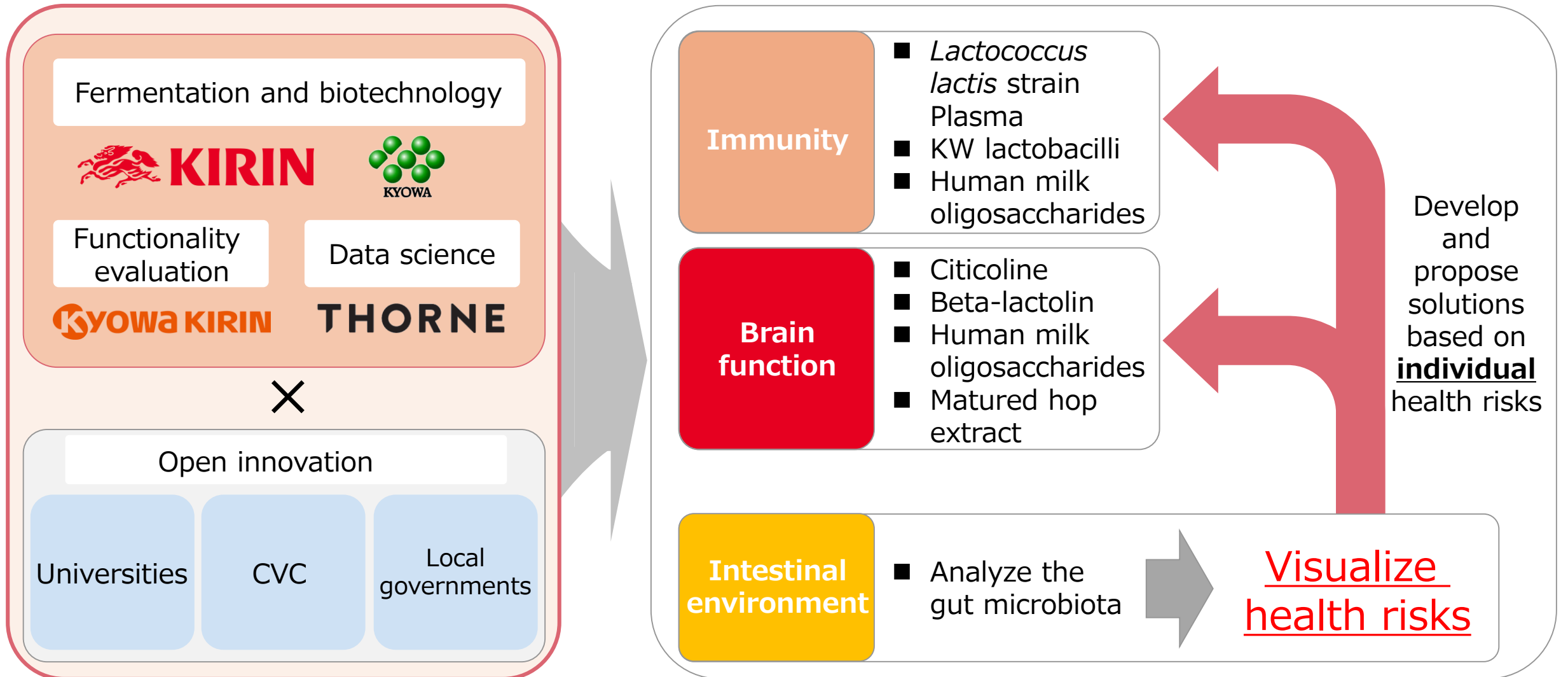


17. Leveraging our strengths to serve consumers



19. Three key domains in the health & well-being domain

Leverage the Group's strengths to innovate in three key domains



20. Research on gut microbiota

The human gut contains approximately 1,000 types of intestinal bacteria, about 40 trillion of which are known to be closely linked to a variety of diseases and health conditions

By examining the gut flora, we can gain a picture of **each individual's** health status

Different people have different flora

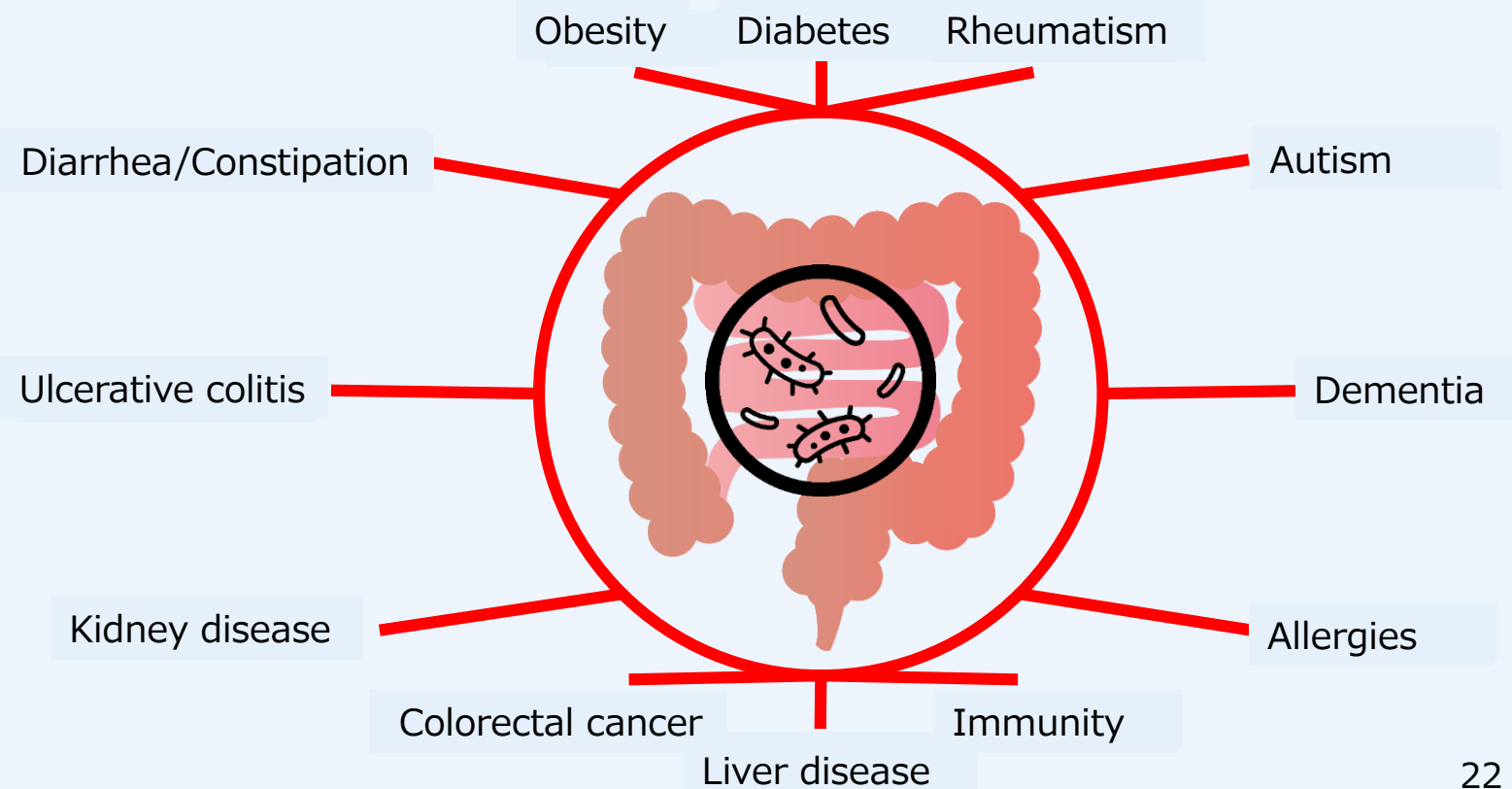
Estimating various health risks based on individual gut flora

Response to individualized needs

Latest research findings

- Measuring intestinal bacteria and metabolites allows early diagnosis of colorectal cancer

Nat Med. 2019 (25) 968-976



21. Study of the gut microbiota at Kirin

Live intestinal bacteria are cultured using an artificial colon model (the only device of its kind in Japan)



Human intestinal cells are cultured using iPS cells (analyzed with Mini-Intestine*)

* A mini-organoid of the intestine developed by the National Center for Child Health and Development



FANCL

Analyze gut microbiota in greater depth
Develop/use useful substances with novel effects

Expanding into the allergy domain
in collaboration with
academia and foreign start-ups

Invested in Siolta, a company developing
prophylactic and therapeutic drugs for
allergies using a cocktail of live bacteria
derived from intestinal bacteria

Siolta
Therapeutics

×

Kirin and Juntendo University have set up a
joint research course to promote the
development of new methods for the
prevention and treatment of allergic conditions



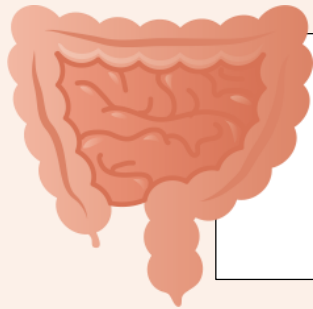
順天堂大学

22. Problem-solving based on gut microbiota

■ Investigating health status based on gut microbiota



Identify individual solutions



Gut bacteria
Number:
about 40 trillion
Number of genes:
more than 2 million species

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■ Kirin's analytical technology and useful substances



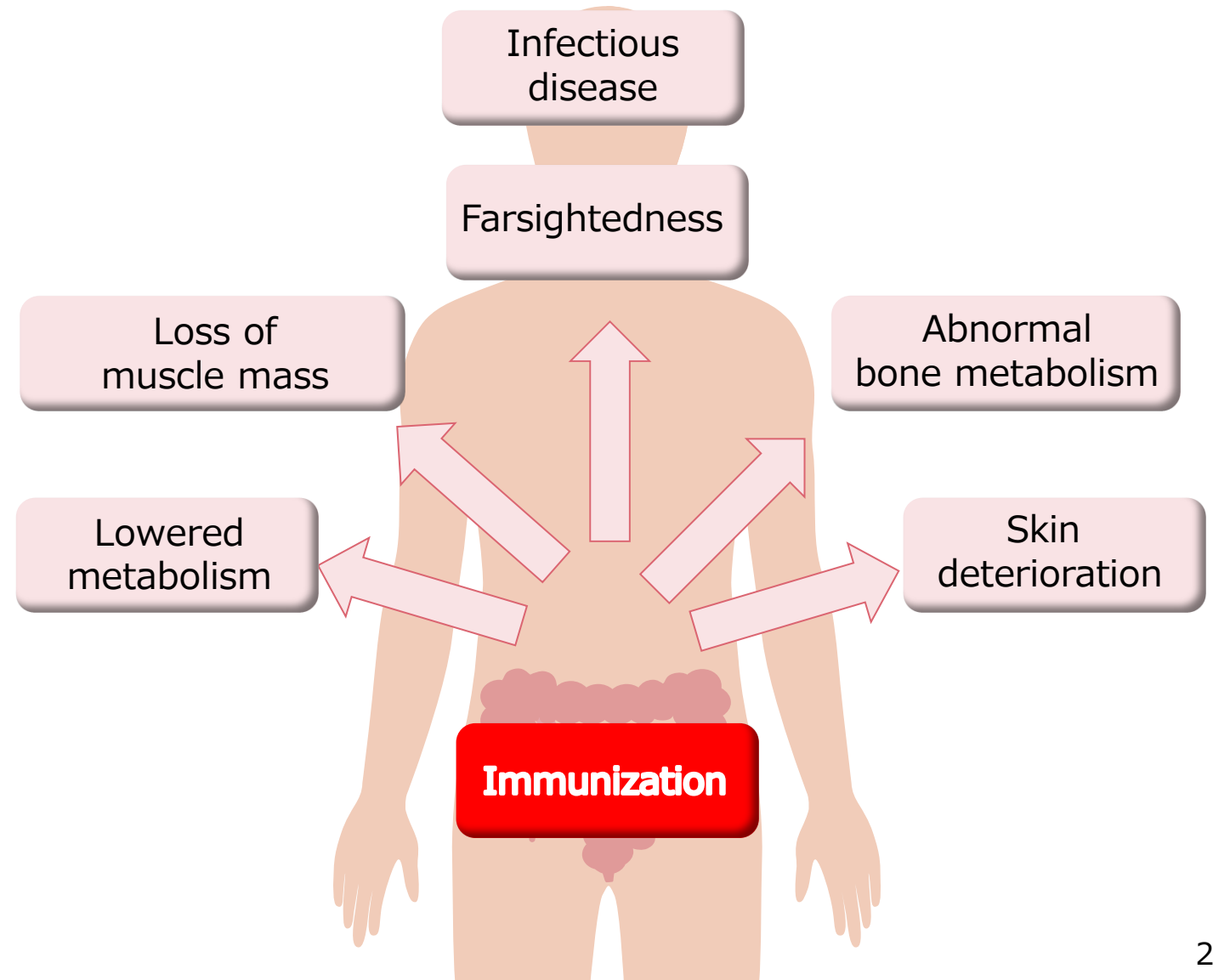
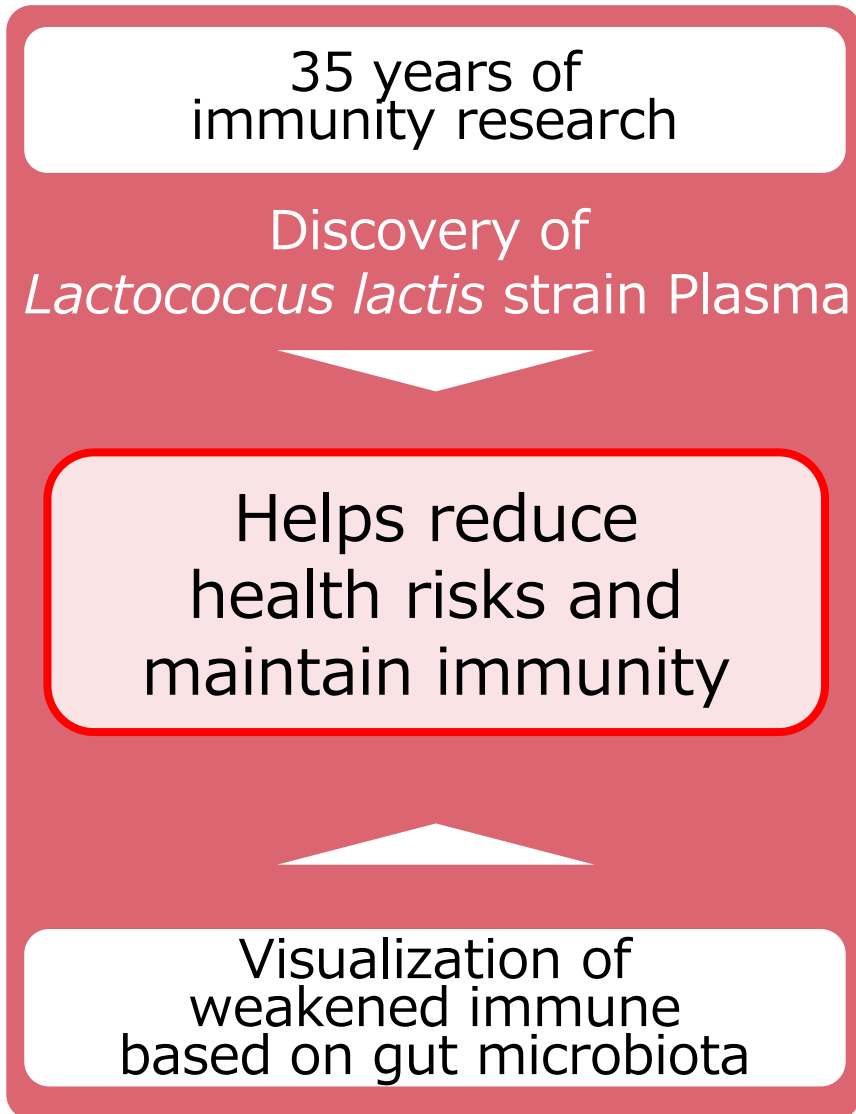
Health-promoting
substances

Data science

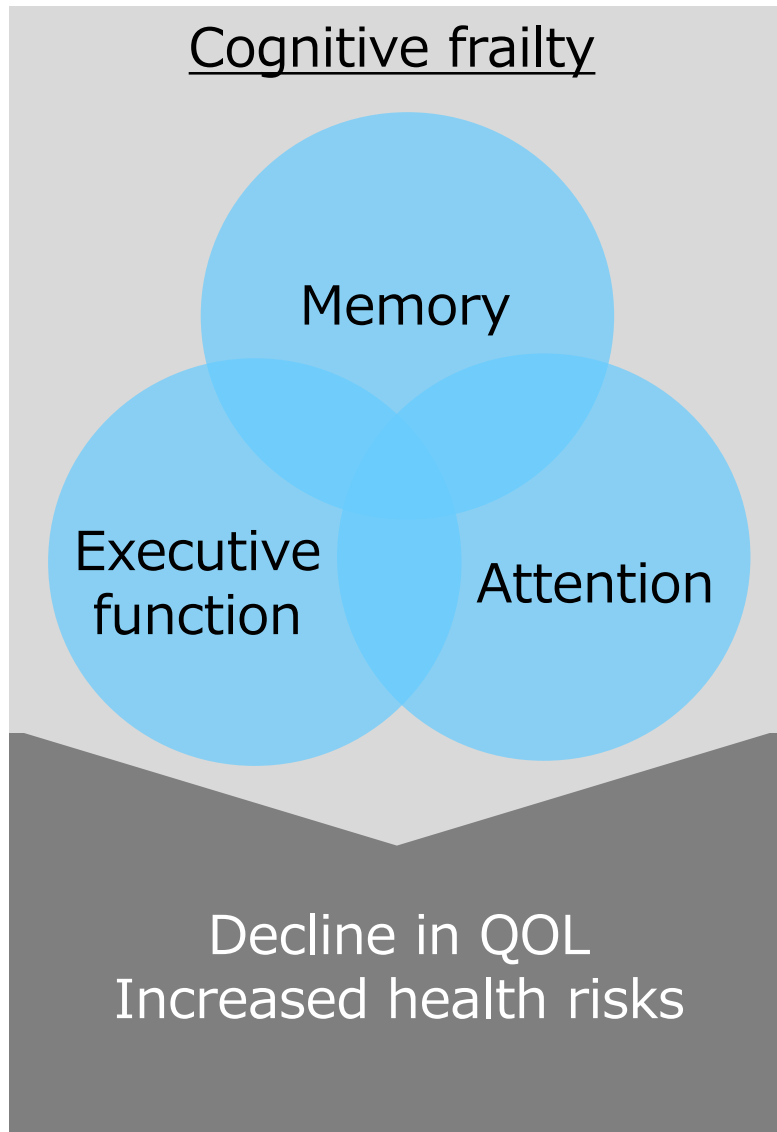
Production
technology

We improve people's QOL by visualizing the health risks faced by each individual based on their gut microbiota and proposing appropriate solutions that allow identifying needs early on

23. Immune function as a key domain of focus



24. An example of application to brain function as a key domain



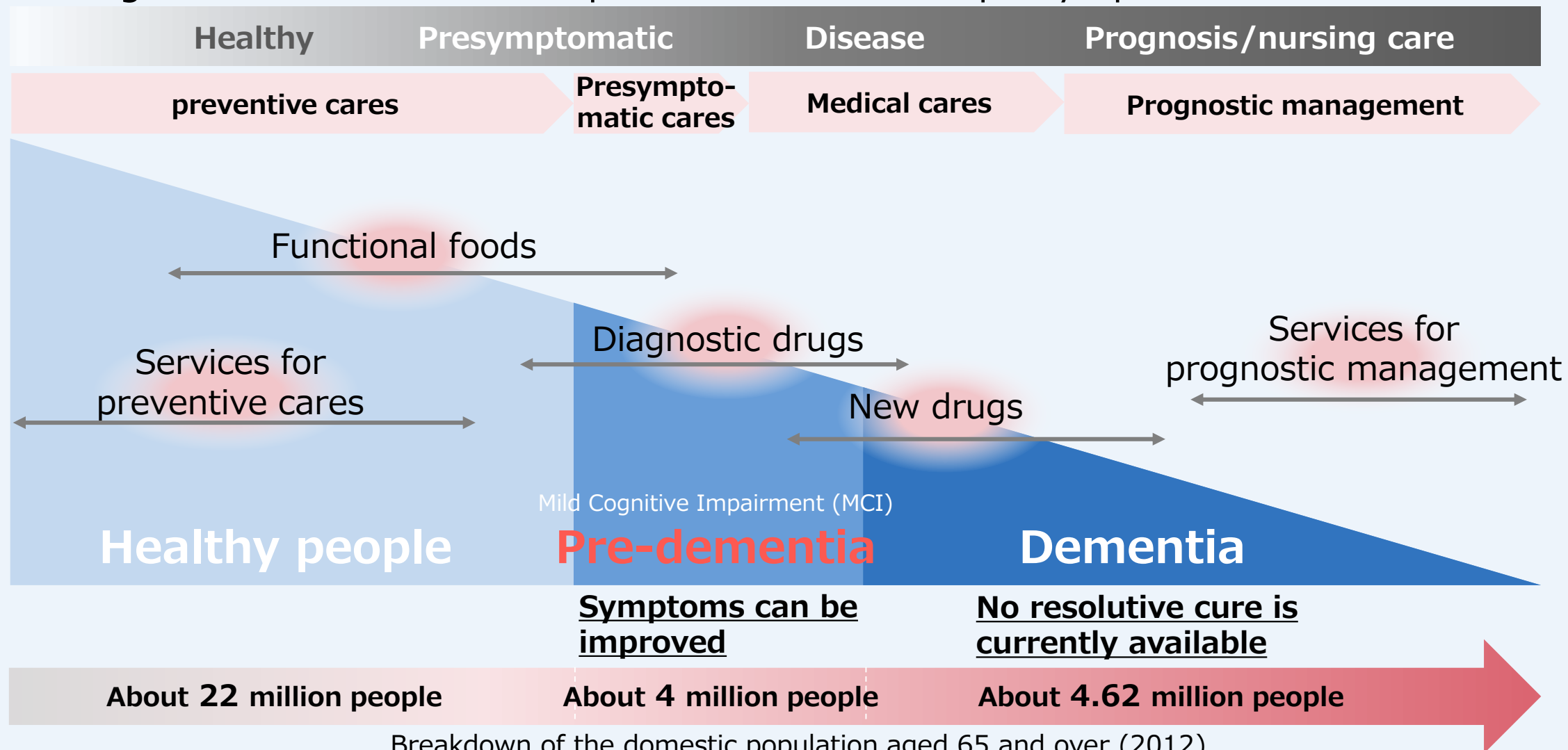
Early detection of health risks based on gut flora

Useful substances	Mechanism	Products envisioned
Citicoline	Serves as a precursor of brain cell components	Energy drinks Tablets Pharmaceuticals
Beta-lactolin	Increases neurotransmitters	Beverages Dairy products
Human milk oligosaccharides	Increases substances involved in memory learning functions in the brain	Milk powder Tablets
Matured hop extract	Increases neurotransmitters via the vagus nerve	Confectionery

Helping maintain and improve QOL

28. The importance of early action

At the presymptomatic stage, the risk of developing dementia is difficult to ascertain, making it difficult to administer preventive cares and presymptomatic cares.



Breakdown of the domestic population aged 65 and over (2012)

"On the Comprehensive Promotion of Dementia Countermeasures" Ministry of Health, Labour and Welfare (Reference)

Awareness of dementia prevention



Figure 1-1 Concerns about dementia

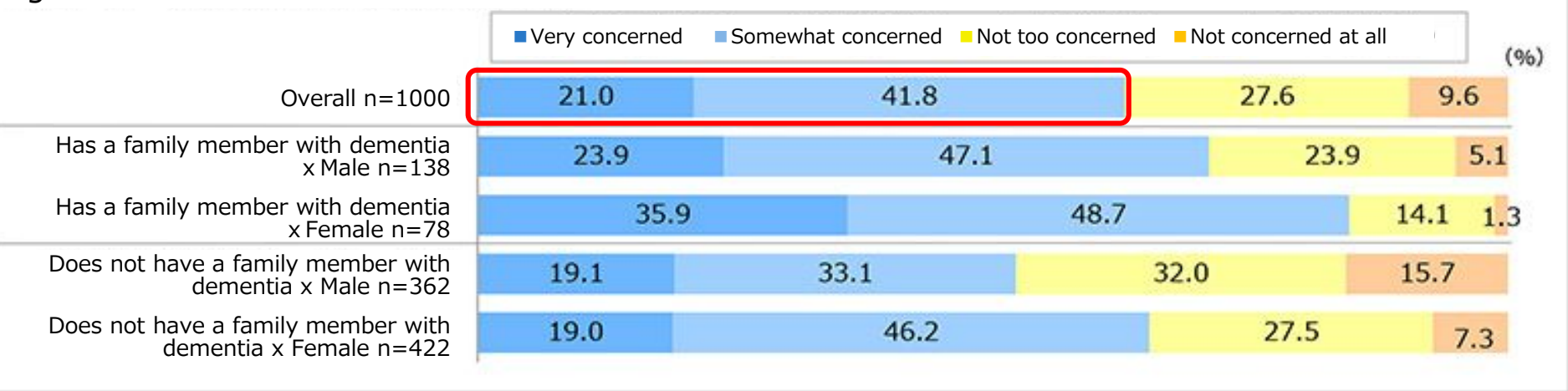
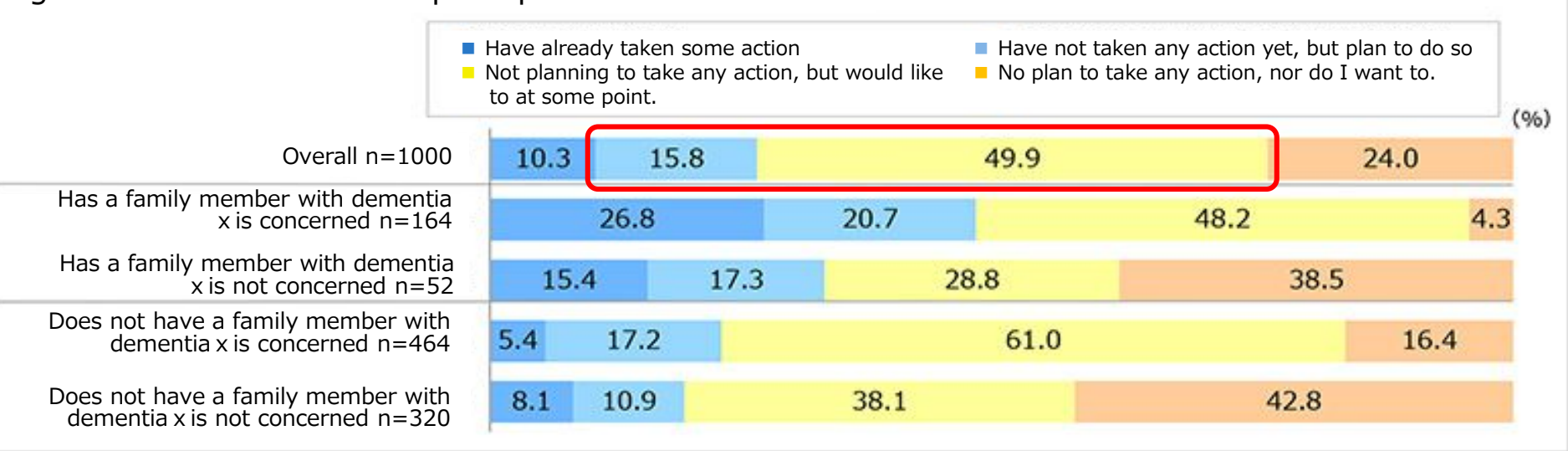


Figure 1-2 Awareness of steps to prevent dementia

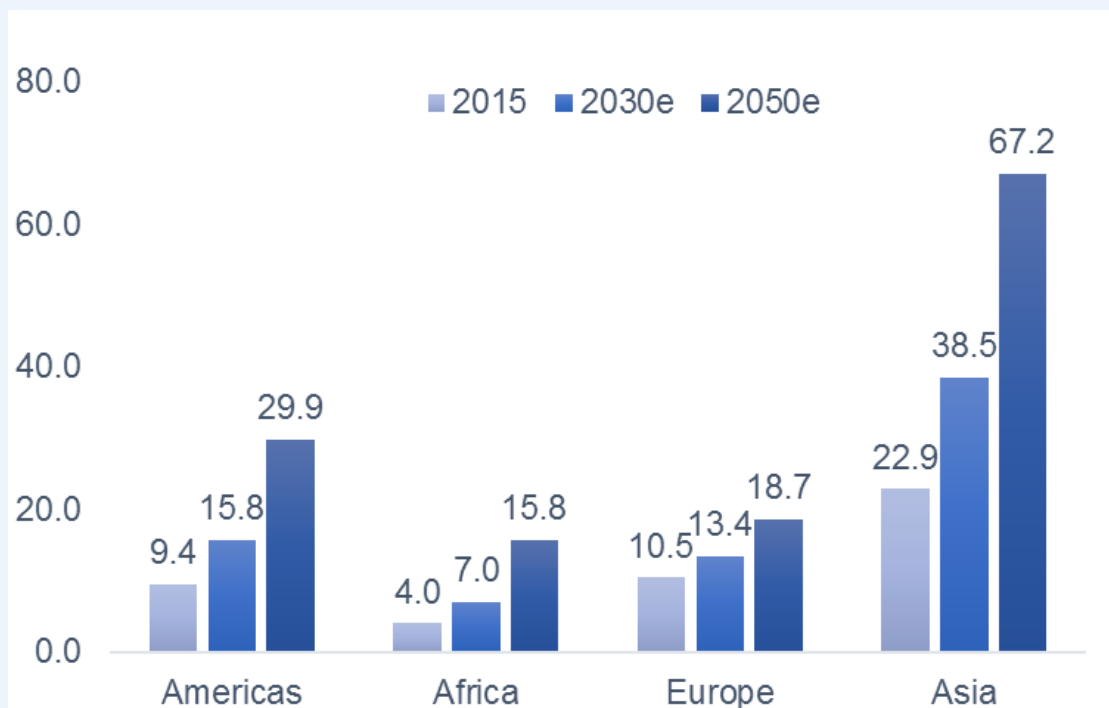


30. Number of patients with dementia and market size

This is a 20 billion yen market in Japan, and it is expected to expand further as needs emerge.

Unit: millions of people

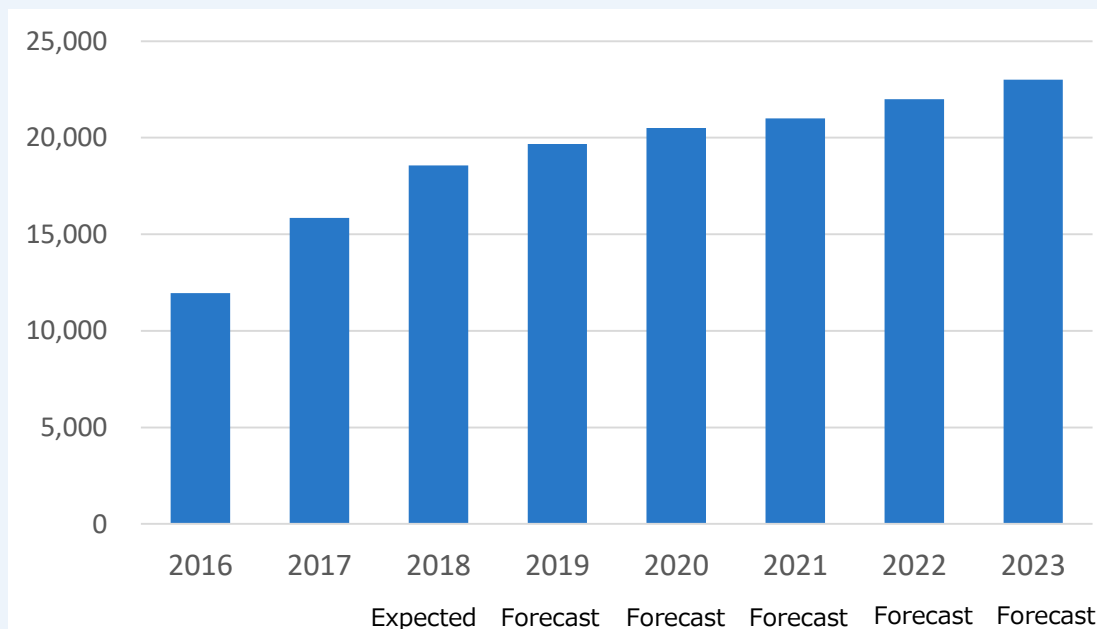
Number of patients



Source: Alzheimer's Disease International - World Alzheimer Report

Unit: million yen

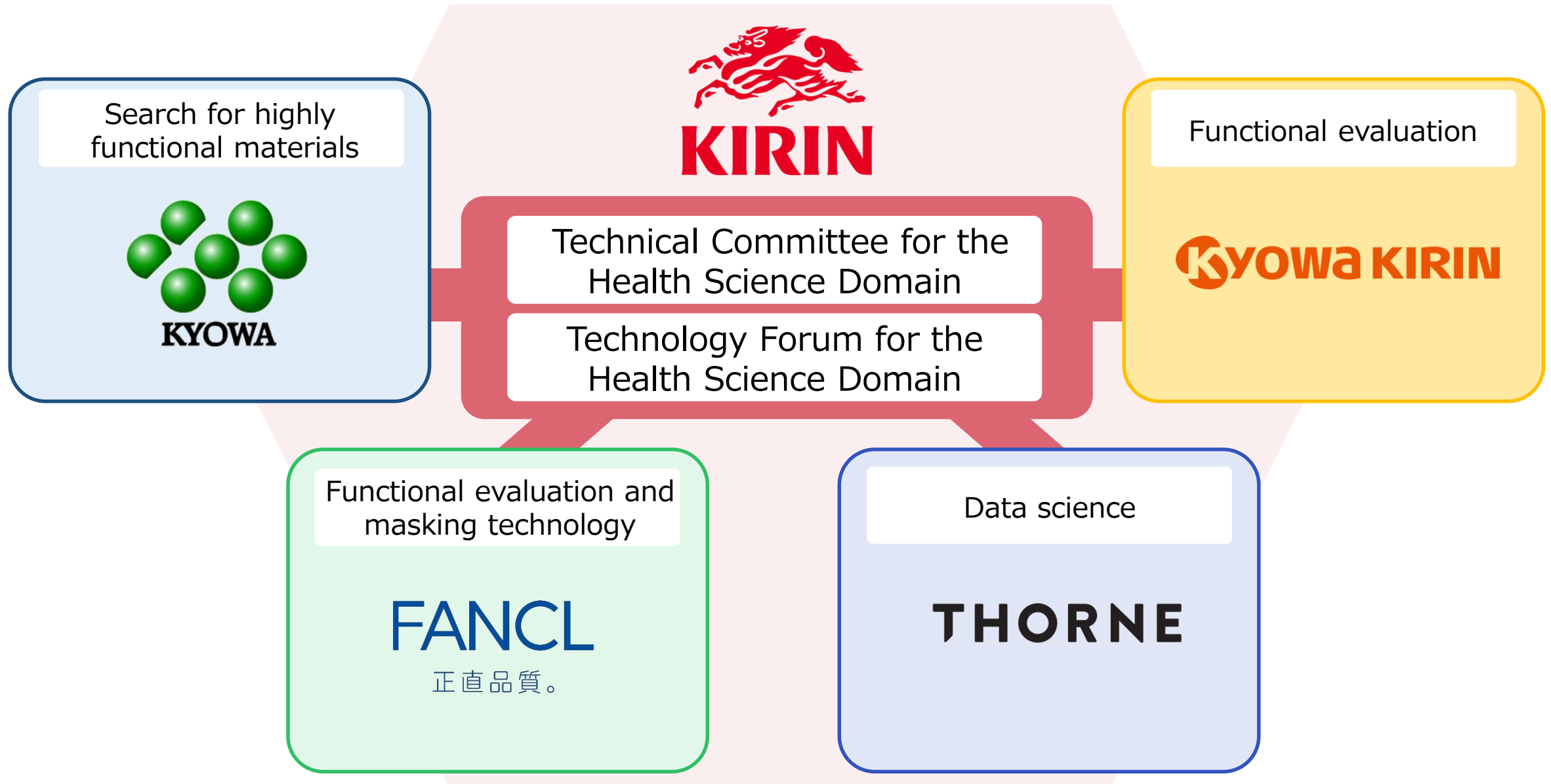
Domestic market size (food and supplements)



Health & Beauty Foods Marketing Handbook 2019 Summary:
Cognitive Function Support Market, Fuji Keizai

Further opportunities in the global market

31. The Group's R&D network in the health science domain



32. Collaboration with Kyowa Hakko Bio and FANCL

Microbial breeding technology

Technology to create microorganisms that produce the desired ingredients



Yeast
Lactobacilli



Amino acid-producing bacteria

Industrialization technology

Technology to realize safe, secure, and large-scale production



Liquids
Blending, flavoring and stabilization



Solids

FANCL

Dermatology and formulation technology
Preparation and masking technology

Channels and products

Combining technologies to create new value



BtoC
Beverages



BtoB
Materials

FANCL

BtoC, directly operated stores, EC
Supplements, skin care product



33. Open innovation

Universities

Kirin and Juntendo University have started a joint research project on intestinal bacteria therapy

~ Aiming to develop new methods for the prevention and treatment of allergic diseases ~



順天堂大学

Partner organizations for research on *Lactococcus lactis* strain Plasma

- Riken
- National Institute of Infectious Diseases
- Tokai University
- Iwate Medical University
- Juntendo University
- Miyazaki University
- David Geffen School of Medicine at UCLA

CVC

CVC fund “KIRIN HEALTH INNOVATION FUND” established

~ First investment made in U.S.-based Siolta ~



Siolta
Therapeutics

Local governments

Specified clinical trial on beta-lactolin in mild cognitive impairment (MCI) started

~ Will help solve the challenges of an unprecedented aging society; in collaboration with Hamamatsu City and the Seirei Social Welfare Community ~



Hamamatsu City



34. Delivering CSV through technology

