Building Strength and Expanding Portfolio in Vaccine Research

December 13, 2023

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Shionogi & Co., Ltd.

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Agenda

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SHIONOGI's Vaccine Research

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From STS2030 Revision
(partially revised)

Infectious Disease Business Policy

Establish a business model for each area to achieve continuous growth

Build a sustainable business model

Acute infectious diseases (COVID-19, influenza, etc.)

Global growth of therapeutic drugs

- Continued research and development activities (Ensitrelvir, Xofluza)

Total care actions

- Achieve growth in the diagnosis, vaccine, and wastewater monitoring businesses

Antimicrobial resistance (AMR)

Work with society to create sustainable markets

- Roll out cefiderocol globally
- Introduce push and pull incentives

Build a stable business base by contributing to large numbers of patients

Infectious diseases requiring a long period of treatment

Cultivate new markets that address unmet needs

- Provide new solutions for HIV infection
- Develop a new drug (olorofim) against highly lethal fungal infections
- R&D of new treatments for infectious diseases with high unmet needs (tuberculosis, malaria, nontuberculous mycobacterial diseases)

Total care, including vaccines

Grow vaccines into the next earnings driver as a core business

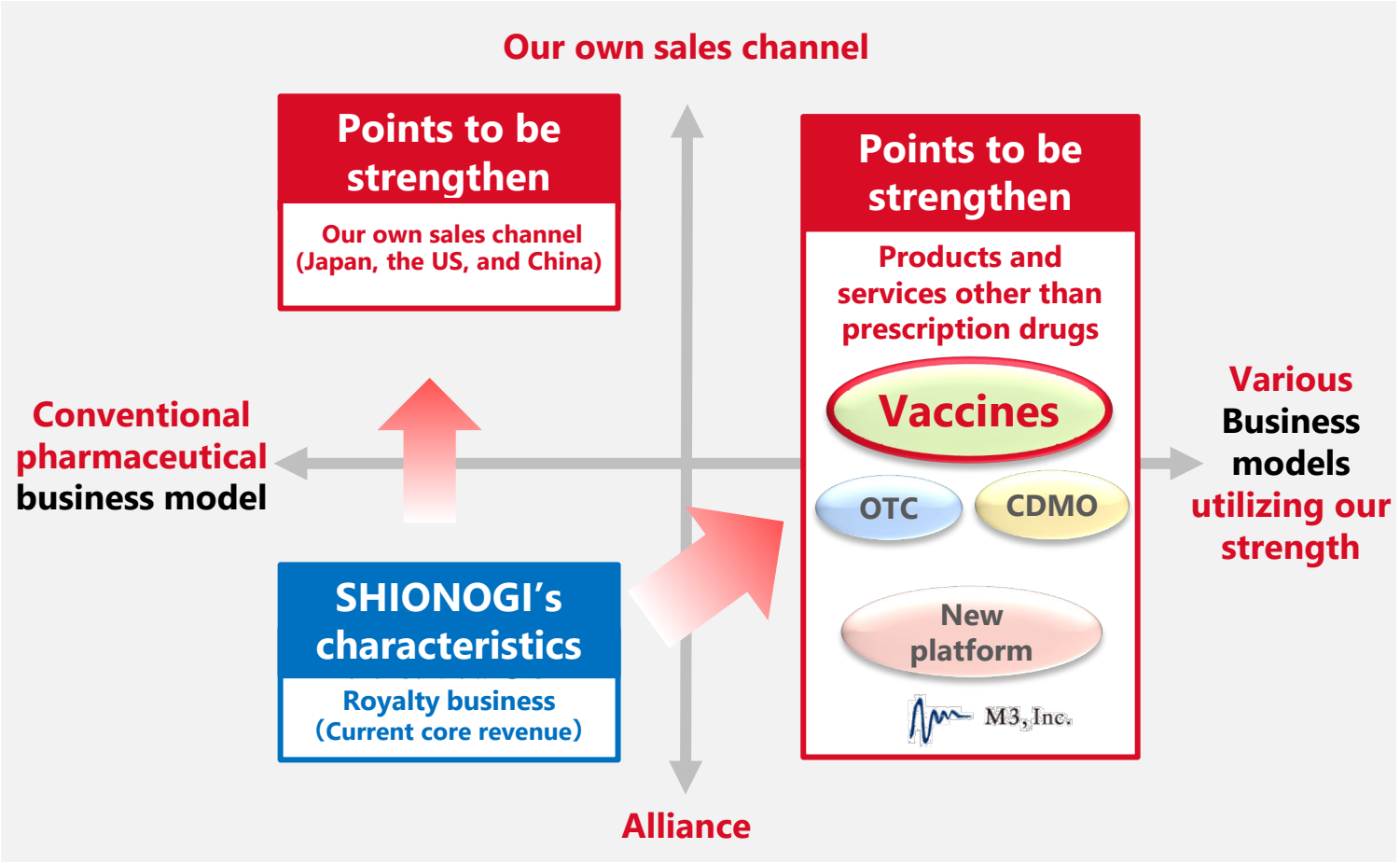
- Launch COVID-19 and influenza vaccines
- Expand the business to Asia and across the world
- Establishment of new technologies that will be our strength (nasal, universal vaccines)

Strengthen diagnostic capabilities

- Provide simple diagnostic solutions (home diagnosis kits, etc.)

Positioning of Vaccines in the Medium-Term Business Plan STS2030

Building stable business foundations that can contribute to the health of many patients



Entry into the vaccine business

- Expand the infectious disease business portfolio
  - Aim for sales of 100 billion yen in 2030
- A business that does not rely on patents
  - No entry into the generics market
- Business that targets healthy individuals
  - Targets all of humanity, which differs from pharmaceuticals that target "patients"
- New entry into this area is high risk
  - Obtaining know-how by acquisition of UMN Pharma Inc,.

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SHIONOGI's Experience to Date in Vaccine Business

Vaccine business is steadily progressing toward our 2030 vision

	STEP 1: Entered the vaccine business (2017—2020)	STEP 2: Advanced R&D of S-268019 (2020—2022)	**Advance research of vaccines further (2022—2023)**
Building a vaccine research base			
Research	• Started creation of influenza vaccine building on experience in drug discovery for the treatment of influenza	• By applying our drug discovery research capabilities in the areas of infectious diseases and immunity, created S-268019 • By merging in-house technology and external collaboration, develop vaccines able to broadly cover mutant strains	• Filing application for S-268019 • Clinical studies for vaccine of the XBB1.5 strain are in preparation • The antigen for universal vaccine was identified • The research for nasal vaccine was adopted by SCARDA
Capital alliance with UMN Pharma		**Gaining know-how in vaccine production**	**Large-scale manufacturing at UNIGEN**
Manufacturing	• Acquisition of 'rhabdovirus-free' insect cell culture techniques • Acquired manufacturing and research base of drug active ingredients	• In-house process from antigenic search to GMP study drug manufacturing (UMN Akita Plant) completed • Acquired experience and knowledge in manufacturing of biopharmaceuticals	• At a 16,000L-scale manufacturing for S-268019, a conformity certification was obtained • Facilities and process were optimized in accordance with characteristics of cells and antigens

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Creation of S-268019 and Resolution of Manufacturing Issues

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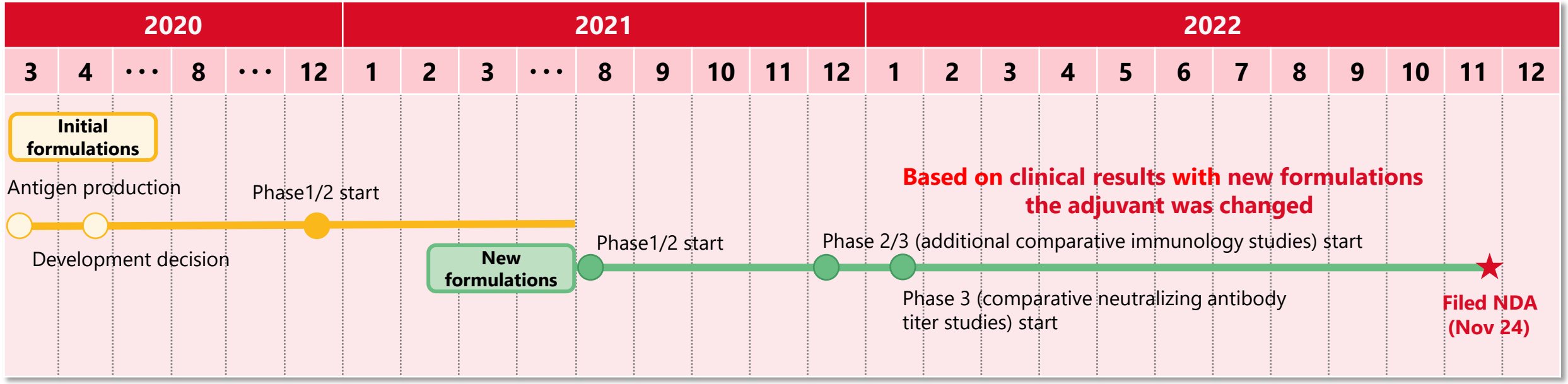
S-268019: The First Vaccine Development in SHIONOGI's History

Less than 3 years from program initiation to filing

Collaborative research with National Institute of Infectious Diseases (NIID) and Kyusyu University (Kyoto University at present)



- **Approximately 4-months from the decision to change adjuvant to the start of the second Phase 1**
  - Explored the combination of various adjuvants and antigens concurrently with Phase 1
- **Construct a seamless and rapidly assessment system for mutant viruses**
  - Systematized monitoring, evaluation, and sample analysis for arising variant strains of the virus

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S-268019: Features identified from R&D efforts

Accumulation of knowledge related to the recombinant protein vaccine

Versatility

- This combination of recombinant protein and adjuvant demonstrates increased antibody titer for variant strains
- Freely customize to customize glycan modifications and amino acid sequence design
  - ➢ Application to universal vaccine

Durability

- This combination of recombinant protein and adjuvant shows durability of neutralizing antibody titer
- Induce durable memory B cells
  - ➢ Immediate antibody production after reinfection with virus

Adjuvants

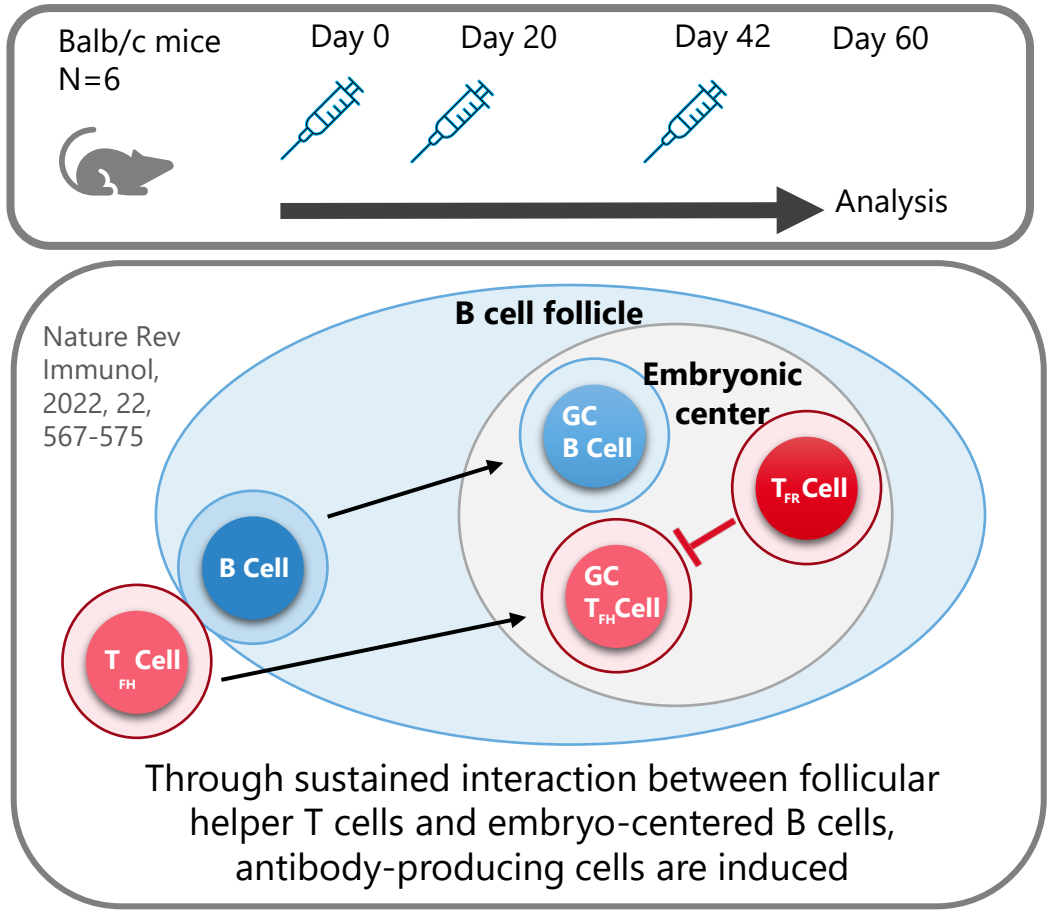
- Built skills for adjuvant design, selection, and production
- Continue to optimize and develop next generation adjuvants

Stability and Safety

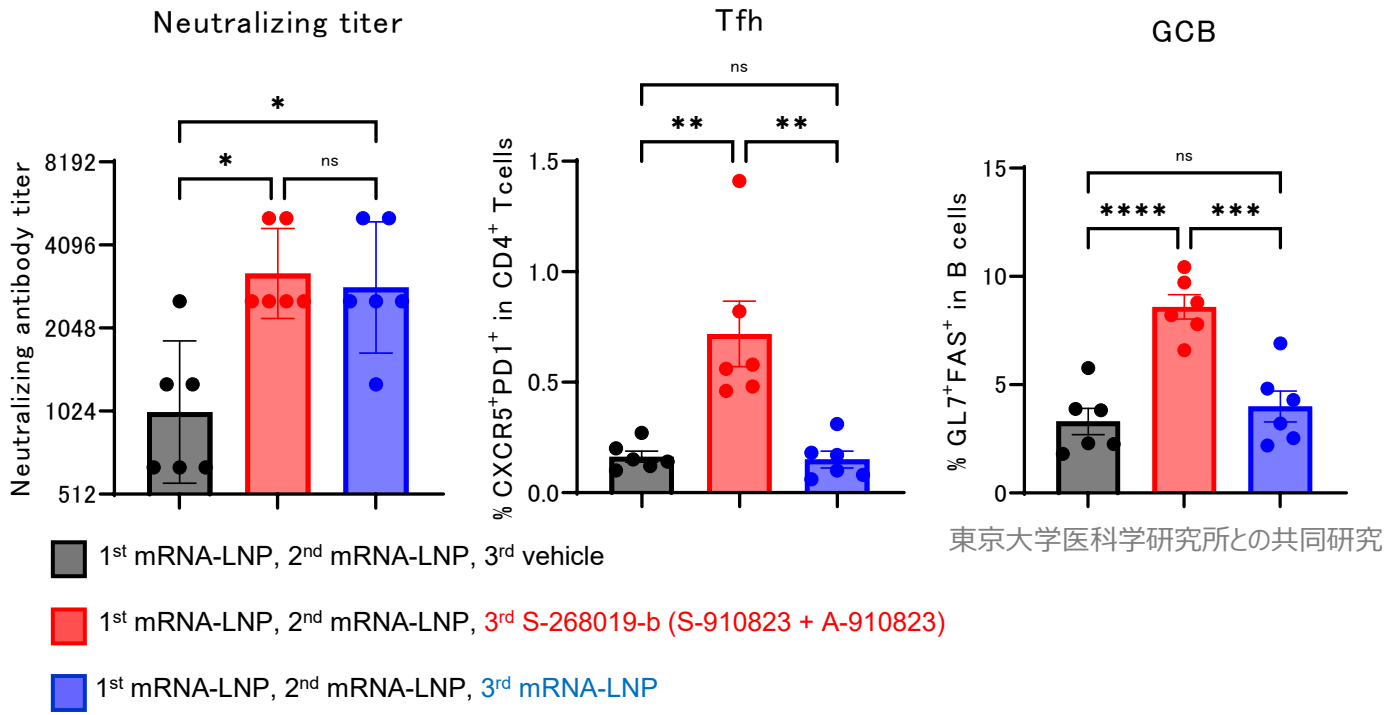
- technology with established safety
- Can be stored at 4℃ with a long shelf life
- Rhabdovirus-free baculovirus antigen production technology using BEVS system of UMN Pharma

S-268019: Increased Efficacy of Vaccine in the Presence of Adjuvant

Superior adjuvant improves the vaccine's efficacy



Through sustained interaction between follicular helper T cells and embryo-centered B cells, antibody-producing cells are induced



東京大学医科学研究所との共同研究

Higher induction of germinal center B cells (GCB) mediated by follicular helper T cells (Tfh) compared to mRNA

2023 Feb 20:14:1116238. doi: 10.3389/fimmu.2023.1116238. eCollection 2023.

* T follicular helper cells (Tfh); a subset of T helper cells that are critical for germinal center formation in immune response, selection of high-affinity B cells, and differentiation of memory B cells and plasma cells

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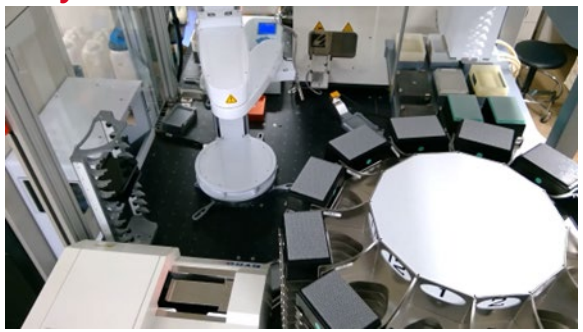
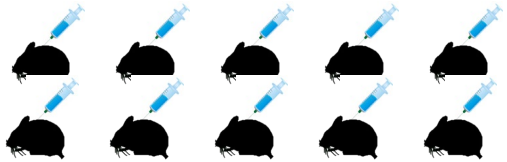
SHIONOGI's Strength: Creation of Antigen SAR* Platform

Antigen SAR platform construction similar to small molecule drug creation

- Enhanced productivity by automation
- Establishment of a rapid evaluation system for variant strains

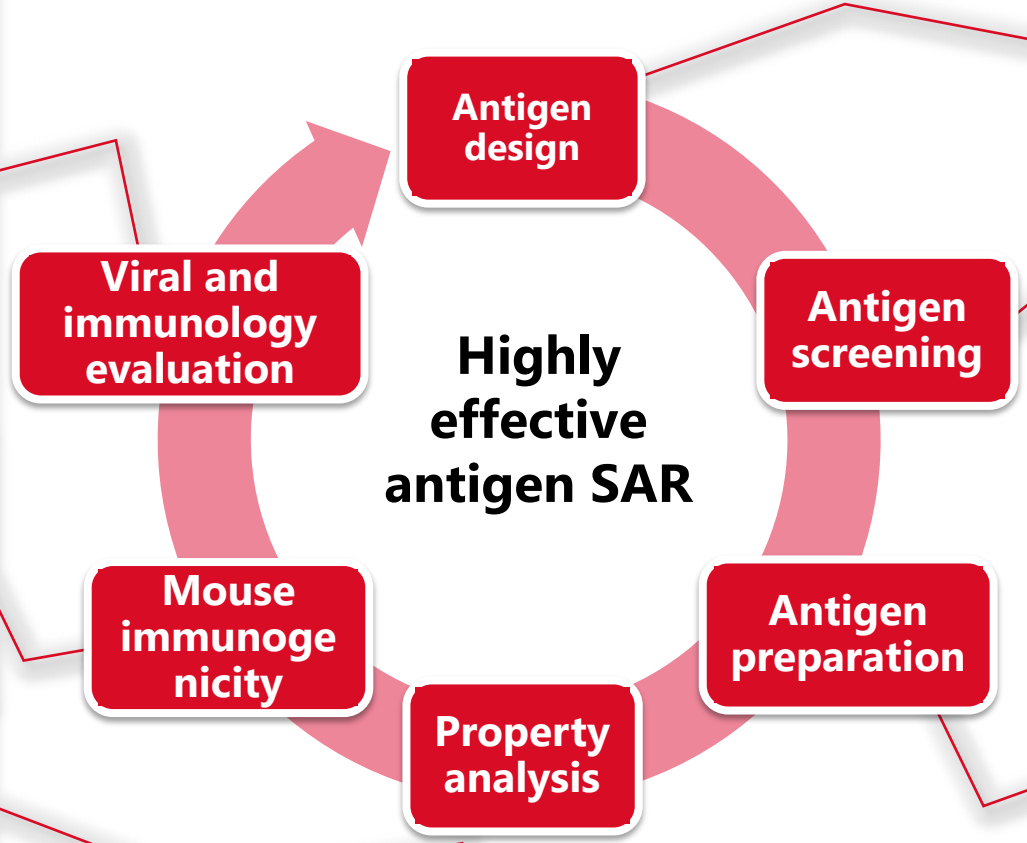


Establishment of an efficient evaluation framework



Consolidated multiple evaluation system considering manufacturing process

SDS-PAGE, MP, DLS, DSF, DSC, (Glyco) Proteomics



Introduced latest technology and knowledge

KOTAI

A venture enterprise that provides cutting-edge technologies and knowledge in information and structure analysis as well as bioinformatics in immunology

- In silico structure prediction of large molecules
- Established enzyme display technology

Displaying antigens on enzymes

Significant improvement in expression system/purification methods

- Established Expi293 expression system
- Introduced spin column purification

* Structure-activity relationship

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SHIONOGI's Strength: Vaccine Antigen and Formulation Production System

Builidng stable manufacturing and supply capabilities of investigational vaccines

R&D process for recombinant protein by BEVS*

R&D process

Construction of transfer vectors	Construction of virus bank	GMP manufacturing	Commercial manufacturing
Process development	Manufacture of specimens for GLP (Engineering run)		
Consideration of scale up, transferring technology to factory			

Obtained ability

Preparing in-house implementation and evaluation system from exploration to manufacturing

Leverage experience at UMN Pharma thus far to stably manufacture 500L scale

1. For characteristics of biopharmaceuticals based on higher-order structure, construct analytical methods for exploratory research
2. Establishing an internal system that can handle quality management, characterization analysis, and application for the development of recombinant protein vaccines

Struggled to scale-up to 16,000L, however, have an outlook on large-scale manufacturing after stabilization of culture process

* Baculovirus Expression Vector System

Issues and Solution in Vaccine Antigen Manufacturing

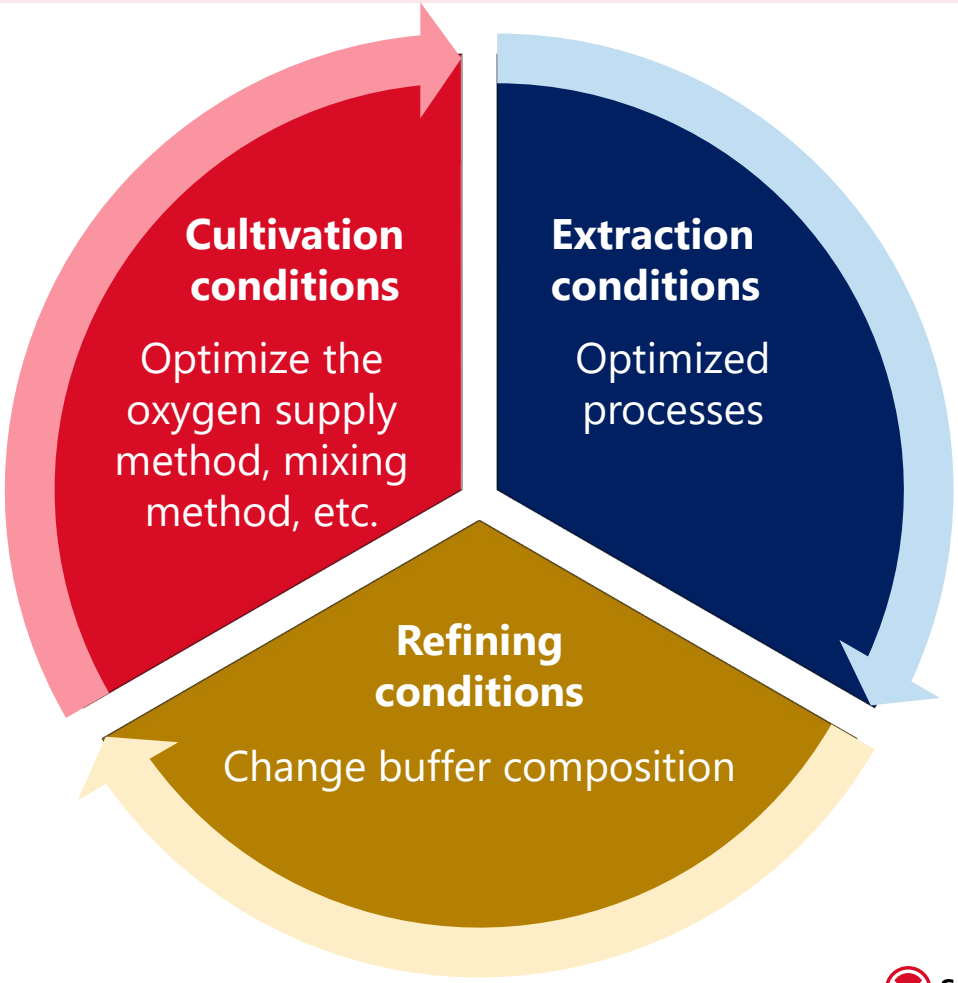
Constructing stable vaccine manufacturing facilities at a commercial manufacturing scale

Issues in commercial manufacturing

- Stable manufacturing when scaled up to 16,000L
- Stable manufacturing when changing the antigen

Solutions

As shown in the diagram on the right, optimize the manufacturing process in line with attributes of cells and antigens and manufacture S-268019



- **Achieved antigen production that met quality standards multiple times in 16,000L scale**
- **Implementing production system for variant strain vaccines**

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Progress of Vaccine Development

Efforts toward building a sustainable business model are progressing

COVID-19 Vaccine

- Establish a recombinant protein vaccine platform and aim for full-scale supply of vaccines against mutant strains in the fall/winter season of 2024
- Actions towards establishing a platform
  - Obtaining approval for S-268019
    - > Continuing discussion: Additional evaluation based on onset prevention trial* data
  - Application for changes based on clinical trial data for XBB1.5 strain vaccine
    - > Developing a monovalent vaccine for the XBB1.5 strain
    - > Scheduled to start case registration in 3Q of 2023

※ Platform
For vaccines that have been established as a platform, if there is a commitment to obtain data on quality, efficacy, safety, and immunogenicity after marketing, it is possible to apply for a complete change to the current recommended strain with the latest quality and preclinical test results

Development of new technology

- Universal vaccine
  - Creation of antigen for universal sarbecovirus vaccine completed
- Nasal vaccine
  - "Research and development of influenza/new coronavirus nasal vaccines" was selected as a vaccine/new modality research and development project solicited by AMED's*2 SCARDA*3

*1 Global Phase 3 NCT05212948
*2 Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response
*3 Japan Agency for Medical Research and Development

Actions towards Creating Future Vaccines

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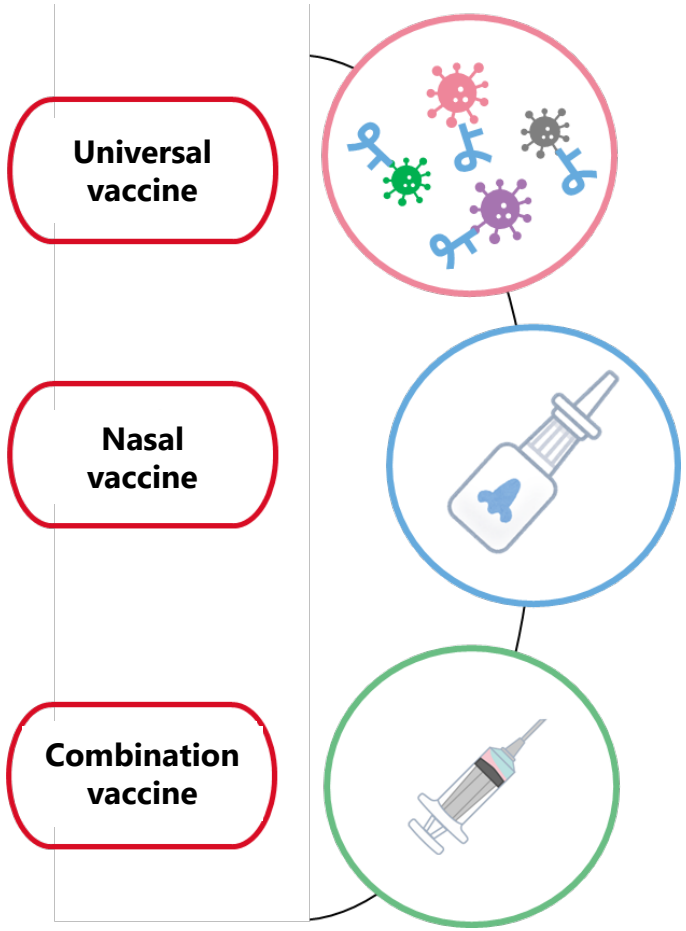
SHIONOGI's Vaccine Research

Advancing new vaccine research utilizing novel modalities at full throttle



Designing truly safe and effective universal antigens to cope with mutant strains to come

- Accepted to the program on R&D of new generation vaccine including new modality application publicly sought by SCARDA* in AMED**
  - Development of universal sarbecovirus* vaccine
- Accelerating collaborative research with KOTAI Biotechnologies, Inc. and National Institute of Infectious Diseases (NIID)

KOTAI
NIID 国立感染症研究所 NATIONAL INSTITUTE OF INFECTIOUS DISEASES

Nasal vaccine to be created by constructing mucosal immunity platform

- Accepted in the program for R&D of new generation vaccine including new modality application publicly requested by SCARDA in AMED
  - Synergy Institute with Chiba University (cSIMVa)
  - R&D of influenza and novel coronavirus nasal vaccine centered on cCHP
- Ongoing collaborative research with Hanavax , Human Mucosal Vaccinology Department at Chiba University, and NIID

cSIMVa
CHIBA UNIVERSITY
HanaVax
NIID 国立感染症研究所 NATIONAL INSTITUTE OF INFECTIOUS DISEASES

Facilitating research for vaccines for respiratory infections other than COVID-19

- Developing preventive vaccines for high-risk patients such as infants, toddlers, and elderly
- Developing combination vaccines to increase consumers' convenience and inoculation rates

* Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response
** Japan Agency for Medical Research and Development

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Creation of Universal Vaccine Antigens

Aiming to create vaccine antigens that are effective for novel variant strains and even the next pandemic

Design of universal antigens

Concepts

- Design a novel antigen using back-calculation from immune factors shown to be induced in humans
- Create vaccines that cover both the then-prevailing SARS-CoV-2 and the next (and next, and next) strain

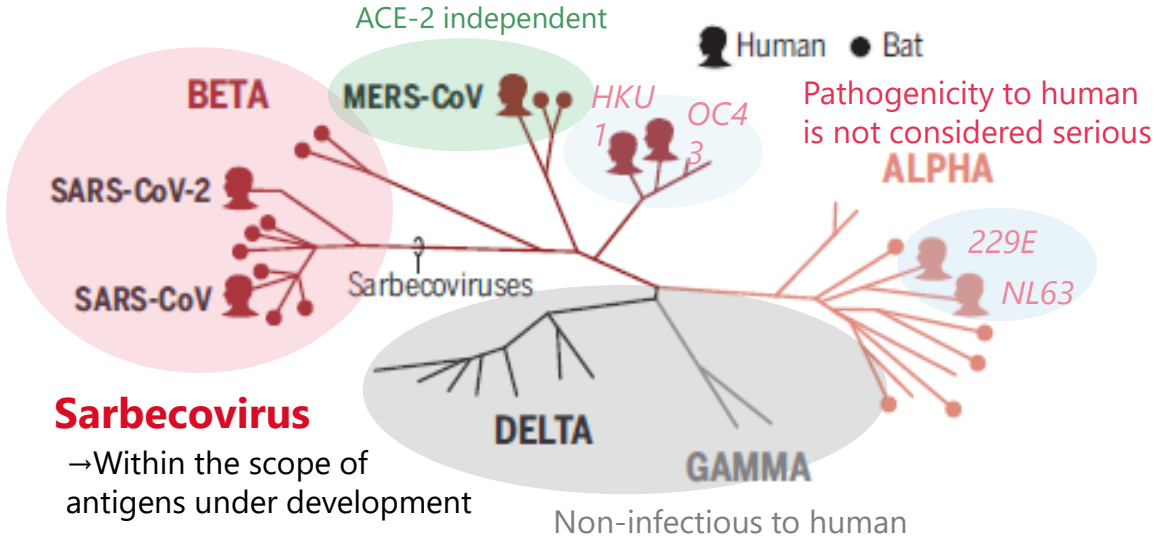
Current status

- Identification of universal sarbecovirus vaccine antigens under development has completed
- On track towards the start of clinical trials in 2024

Effects

- Neutralizing antibody titer increase has been confirmed not only in the original strain of SARS-CoV-2 but also in various mutant strains and even in the strain of SARS-CoV-1 that caused pandemic in 2003
- Data to be published at next R&D Day

Evolutional tree of coronavirus



Points to consider in the design universal antigens

Stabilization of protein structure	Change of dynamic characteristics of proteins
Optimization of versatility	Regulation of epitope

SCIENCE 16 Apr 2021, Vol 372, Issue 6539, pp. 227-231

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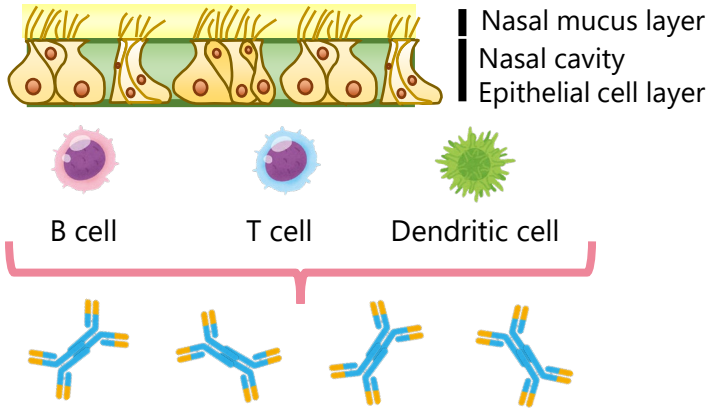
Nasal Vaccines: Difference from Conventional Muscularly Injected Vaccines

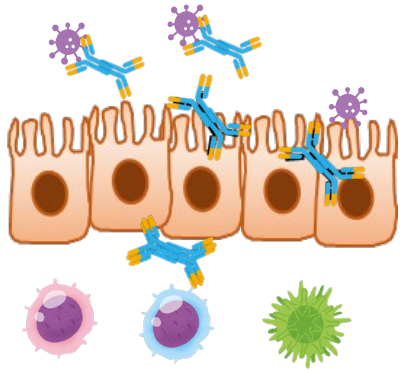
Protect against infections by inducing IgA in the nasal mucosa, and prevent systemic spread of viruses

Conventional vaccine	IgG induction ⇒ Being able to prevent worsening or onset of symptoms in systemic immunity, but unable to prevent infection itself
Nasal vaccine	IgA induction ⇒ By inducing mucosal immunity in addition to systemic immunity, being able not only to reduce the severity of infections and prevent viral transmission but also to prevent the pathogenic infection itself

Induce antigen-specific secretory IgA in respiratory mucosa

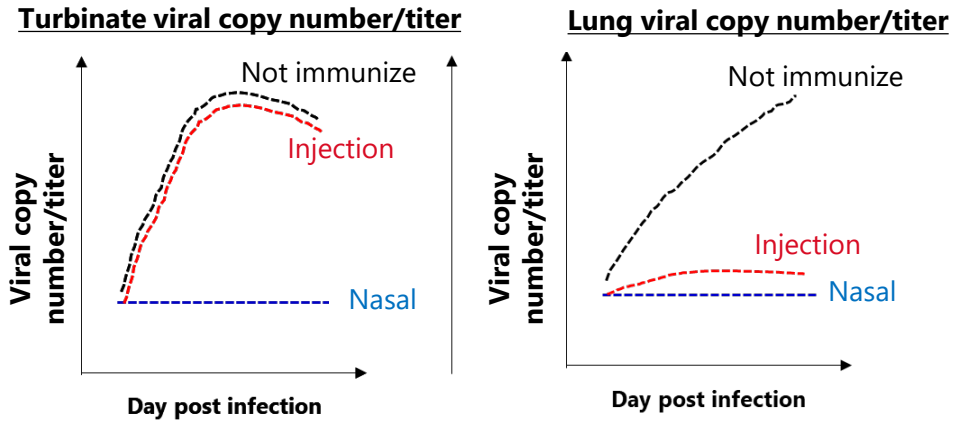


Reduce viral load entering to body from respiratory mucosa



Decreased viral load in lung due to the reduction of viral load entering to body

Graphical image after vaccination



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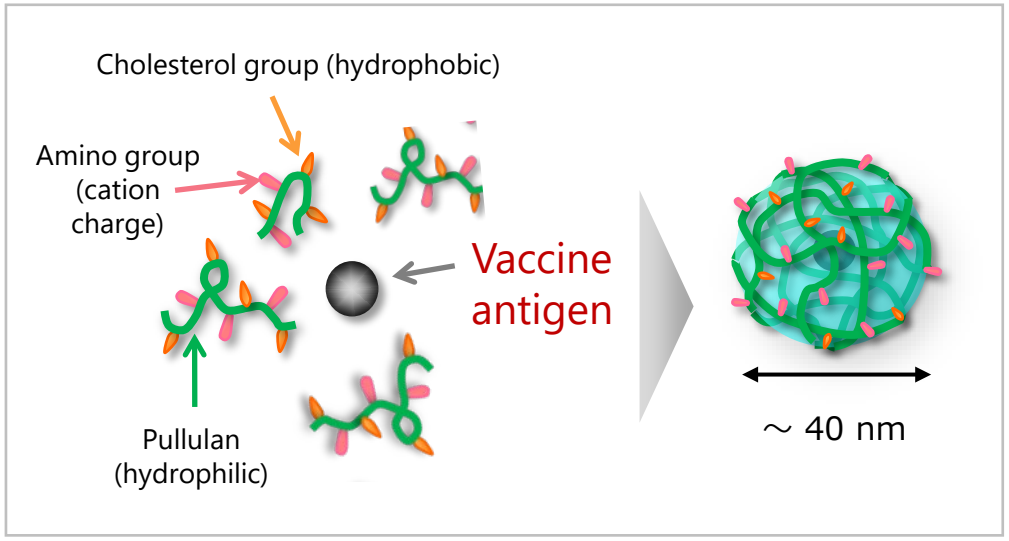
Nasal Vaccine: Usefulness of cCHP* Carrier Adopted from HanaVax Inc.

Being able to induce effective mucosal immunity due to prolonged the nasal residence time of the antigen

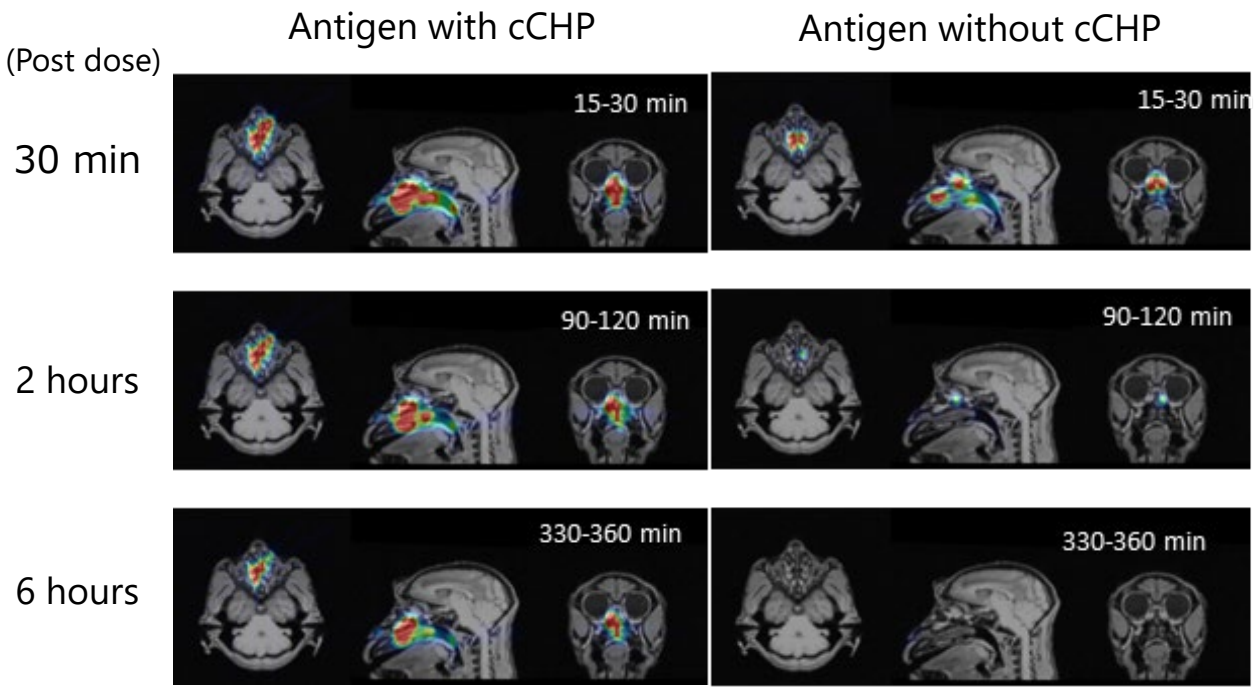
What is cCHP* ?

- Cationic nanogel consists of cholesteryl pullulan
- Compound formation with protein in solution was confirmed

The vaccine antigen was enveloped in cationic nanogel



Prolongation of the nasal residence time of the antigen



The nasal residence time of the vaccine antigen is prolonged

Mucosal Immunology | VOLUME 8 NUMBER 5 | SEPTEMBER 2015 p.1144-

* Cationic nanogel delivery system

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From STS2030 Revision
(partially revised)

Actions and Outlook for the Vaccine Business

Strengthen global supply capabilities while introducing ever more advanced products

Up to FY2025 → **Up to FY2030** → **FY2030 onward**

Establish a track record as a vaccine manufacturer

- Launch COVID-19 vaccine
- Discover and launch influenza vaccine
- Establish a recombinant protein vaccine production framework
- Cooperate with international organizations (e.g., WHO, Gavi*)

Expansion into Asia

- Supply products from Japan to China and ASEAN countries

Gaining competitive edge

- Gain the ability to respond to the 100 days mission: Discover vaccines for SCARDA's core diseases
- Address unmet needs with new approaches and technologies
  - Develop nasal vaccines; develop a universal vaccine; consider new modalities

Global expansion

- Affordable provision to LMICs**
- Provide vaccines with added value to the U.S. and European markets

* Global Alliance for Vaccines and Immunization ** Lower Middle Income Countries

Appendix

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Pipeline: Infectious Disease

as of October 30, 2023

Preclinical	Phase 1	Phase 2	Phase 3		Submission
S-872600 Influenza nasal vaccine	**S-337395** RSV infections		**Olorofim [F901318]** Invasive Aspergillosis	**Ensitrelvir*** COVID-19 treatment	**Ensitrelvir*2** COVID-19 treatment
S-875670 COVID-19 nasal vaccine	**S-892216** COVID-19 treatment		**Cefiderocol** Aerobic Gram-negative bacterial infection (Pediatric)	**Ensitrelvir** COVID-19 prevention	**S-268019*3** COVID-19 Prophylactic vaccine
S-540956 Nucleic acid adjuvant	**S-743229** AMR (Urinary tract infection)		**S-268019** COVID-19 Prophylactic vaccine	**Ensitrelvir** COVID-19 treatment (Ages 5-11)	**Cefiderocol*4** Various infectious diseases
S-554110 Nontuberculous mycobacterial infection				**S-268019** COVID-19 (Ages 5-19)	**Baloxavir** Influenza virus infection (Granules, < 20kg)
S-268023 COVID-19 Prophylactic vaccine (XBB 1.5)					**Baloxavir *5** Influenza virus infection (5-11 years old, treatment and prevention)
S-649228 AMR (Various infectious diseases)					

Change from July 10 to October 30, 2023
S-266023 : Add Code No. S-649228 : Add Code No. S-743229 : Conducting Phase 1

Out license

S-365598 HIV infection	**S -555739 [Asapiprant]** Treatment by suppressing aggravation of COVID-19	**Baloxavir** Influenza virus infection (Pediatric, < 1 year old)	**Baloxavir** Influenza virus infection (Transmission)	**Baloxavir (US)** Influenza virus infection (Pediatric, < 1year old)

: Global development

: Progress from July 31 to October 30, 2023 *,*3 Phase 2/3、Phase 3 ongoing *2 Korea *4 Japan, Taiwan *5 Taiwan

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Pipeline: QOL Diseases with High Social Impact

as of October 30, 2023

Preclinical	Phase 1	Phase 2		Phase 3	Submission
S-540956 Nucleic acid adjuvant	**S-151128** Chronic pain	**S-309309** Obesity	**S-005151*** **[Redasemtide]** Acute ischemic stroke	**S-812217** **[Zuranolone]** Depression	
S-109802 Post-stroke spasticity	**S-588210** Solid tumor	**S-531011**[*2] Solid tumor	**S-005151** **[Redasemtide]** Epidermolysis bullosa	**GRT7039** **[Resiniferatoxin]** Pain associated with knee osteoarthritis	
		BPN14770 **[Zatolmilast]** Alzheimer's disease	**BPN14770** **[Zatolmilast]** Alzheimer's disease	**BPN14770**[*5] **[Zatolmilast]** Fragile X Syndrome	
		S-588410 Bladder cancer	**Rizmoic**[*3] Opioid-induced constipation(pediatric)	**SDT-001** Inattentive ADHD (pediatric)	
		S-588410 Bladder cancer	**ADR-001**[*4] Decompensated liver cirrhosis	**S-588410** Esophageal cancer	
		S-488210 Head and neck squamous cell carcinoma	**S-222611** **[Epertinib]** Malignant tumor	**SR-0379** Cutaneous ulcer	
Out license		**S-723595** Type 2 diabetes			

: Global development

* Global Phase 2b ongoing *2 Phase 1b/2 ongoing *3,4 Phase 1/2 ongoing *5 Phase 2b/3 ongoing

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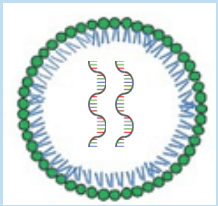
From Top-Line Results of the Phase 2/3 booster Trial for COVID-19 Recombinant-based Vaccine, S-268019 on March 4, 2022 (partially revised)

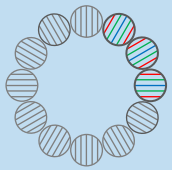
Vaccine Antigen Production Technology

mRNA vaccine
(*COMIRNATY)
(*Spikevax)



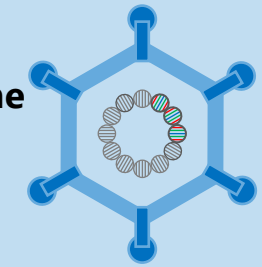
Stabilization by conversion from RNA to DNA

DNA vaccine
(AG0302-COVID19)



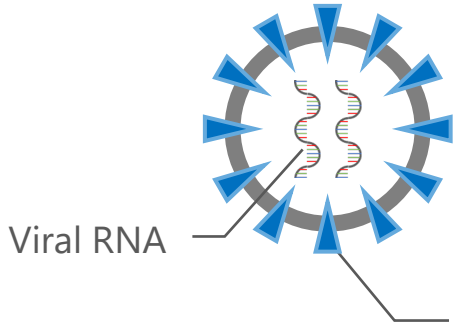
Protection of DNA by shells such as adenovirus

Virus vector vaccine
(*Vaxzevria)
(*JCOVDEN)



New generation technology

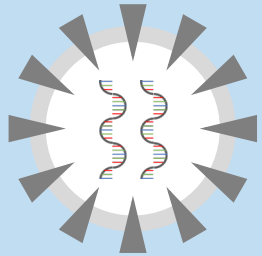
SARS-CoV-2 virus particle
(RNA virus)



Recombinant protein vaccine
(*NUVAXOVID)
(SHIONOGI)

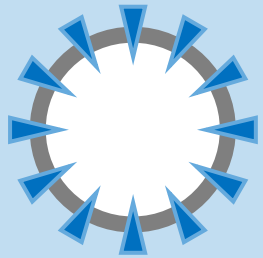
Inactivation of virus by heat/chemical treatment

Inactivated vaccine
(KD-414)



Empty virus particles without genome

****VLP vaccine**
(COVIFENZ)



Traditional technology

* COVID-19 vaccine currently in use in Japan ** virus-like particle

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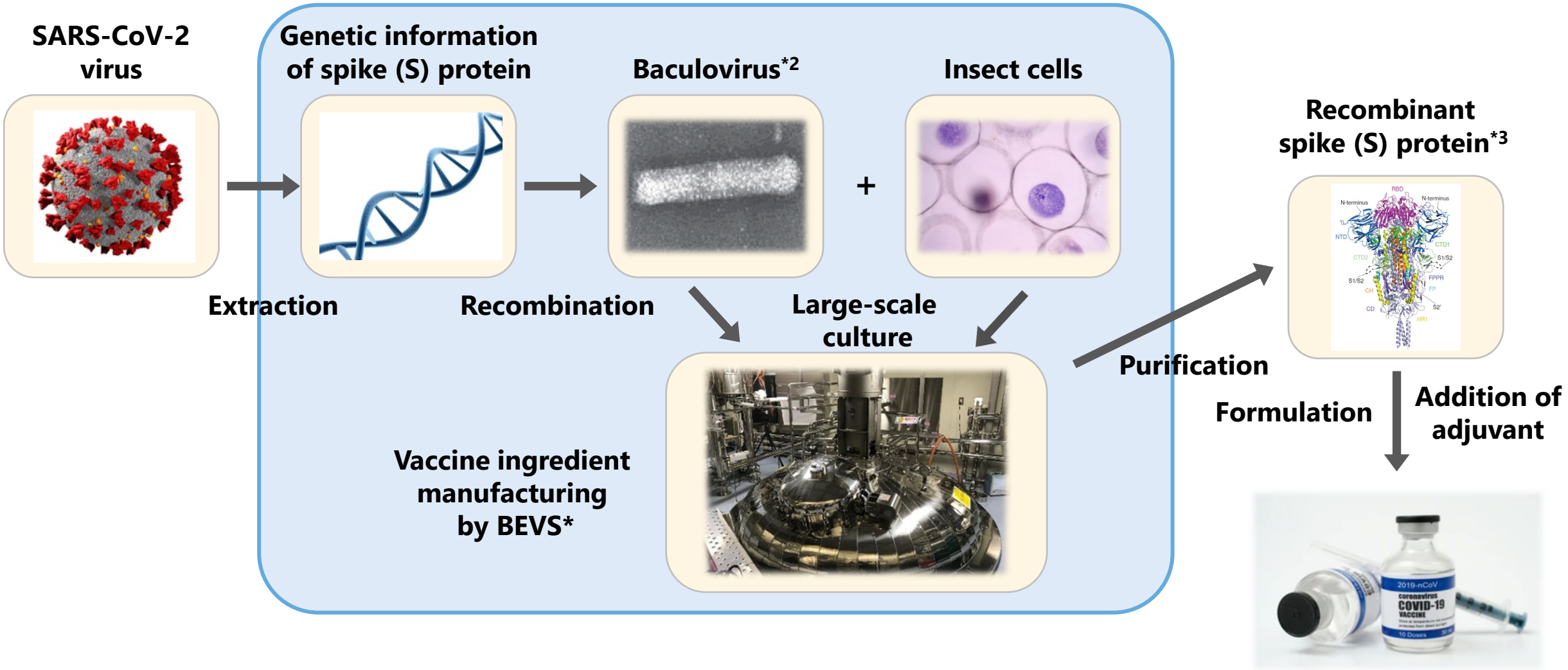
Manufacturing process of recombinant protein vaccine by BEVS*



* Baculovirus Expression Vector System

*2 YAKUKENSHA CO., Ltd.

*3 Science, 2020, 369, 1586–1592, Cai et al.

Forward-Looking Statements

- Forecast or target figures in this material are neither official forecasts of earnings and dividends nor guarantee of target, achievement and forecasts, but present the midterm strategies, goals and visions. Official earnings guidance should be referred to in the disclosure of the annual financial report (*kessan tanshin*) in accordance with the rules set by Tokyo Stock Exchange.
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