Development of mRNA vaccines
Oct 5, 2021  Summary from DS seminar
Vaccine Research Labs., Biologics Division
Fumihiko Takeshita
Vaccine Preparedness

To contribute to society through establishing pharmaceutical technology and manufacturing capability for vaccine preparedness

Stable vaccine supply through in-house manufacturing facility

- DS’s marketed vaccines are being stably supplied from a domestic manufacturing facility
  - Seasonal influenza HA vaccine
  - Live vaccines (measles, rubella, and mumpus)

Vaccine R&D by utilizing innovative modality

- Development of DS-5670*
  - Initiated Ph1/2 study in March 2021
  - DS-5670 utilizes original LNP that efficiently encapsulates mRNA and confers efficient delivery of mRNA to targets
- To build a platform that streamlines development and manufacturing of a variety of LNP-mRNA vaccines for future emerging/re-emerging infectious diseases

To build vaccine manufacturing facilities for future pandemics

- To establish in-house and domestic manufacturing facilities through an enterprise supported by MHLW
- To acquire capability of stable and emergency supply for vaccine preparedness and to become an essential infrastructure for emergency preparedness through collaboration with other organizations in the pharmaceutical industry

*Development of DS-5670 has been supported by AMED and MHLW
Agenda

1. LNP-mRNA vaccine technology
2. COVID-19 vaccine (DS-5670) preclinical data
3. Current status of DS-5670 development and future plan
Manufacturing processes for different vaccine platforms
History of technology development related to mRNA vaccines

- **1961**: Brenner, Jacob, Watson, Meselson - mRNA Isolation
- **1964**: Brenner - Film Hydration method launching liposome industry
- **1968**: Felgner et al. - Lipofection
- **1993**: Martinion - mRNA vaccine determinesCTL response is antigens specific
- **1994**: Bailey and Cullis - Ionizable cationic lipid DOPE for lipofection
- **2005**: Jeffs et al. - Publish T-tube method for plasmid-loaded LNPs
- **2008**: Weide & Pascolo - FDA authorize clinical trial of direct injection RNA Vaccine
- **2011**: Kreiter - F103 improves RNA vaccine efficacy
- **2013**: Pollard - Type I IFN reduces RNA efficacy by s.c. administration
- **2013**: Hekele et al. - First demonstration of sRNA-LNP for rapid response
- **2018**: Onpatro - First mRNA-LNP vaccine approved by FDA
- **2020**: Phase 3 clinical trials of multiple mRNA-LNP vaccine
- **2020**: UK approved mRNA-LNP vaccine for SARS-CoV-2

(Vaccine 9:97 2021, https://doi.org/10.3390/vaccines9020097)
## The use of mRNA as a treatment modality (as of 2017)

<table>
<thead>
<tr>
<th>mRNA modality</th>
<th>No. of programs per R&amp;D phase</th>
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<td><strong>Individualized cancer vaccines</strong></td>
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<td><strong>Replicon RNA infectious disease vaccines</strong></td>
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<td><strong>Protein therapeutics for cancer &amp; CV</strong></td>
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<td><strong>Protein therapeutics for mono-genetic diseases</strong></td>
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<td><strong>mRNA antibody therapeutics</strong></td>
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<td><strong>Ex vivo T cell engineering</strong></td>
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(mRNA Vaccines & Therapeutics 2017: an industry analysis of technologies, pipelines, stakeholders and deals released by La Merie Publishing on June 18, 2017)
Clinical studies assessing mRNA vaccines for infectious disease other than COVID-19  
(as of Aug 2021)

<table>
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<th>Disease target</th>
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<td>LNP</td>
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<td>Moderna</td>
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<td>RSV</td>
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<td>Merck proprietary formulation</td>
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<td>LNP</td>
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<td>Ongoing</td>
<td>Moderna, TranslateBio/SP, BioNTech/Phizer</td>
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(npj Vaccines 5: Article number 11, 2020)
# mRNA vaccine candidates in clinical trials for COVID-19 (as of Sep 24, 2021)

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<tr>
<th>ID</th>
<th>Vaccine platform acronym</th>
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<td>BNT162b2 (S LNP-mRNAs), also known as &quot;Comirnaty&quot;</td>
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<td>MRC/UWRI and LSHTM Uganda Research Unit</td>
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<td>Day 0 + 30</td>
<td>IM</td>
<td>Arcturus Therapeutics, Inc.</td>
<td>Phase 1/2</td>
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</tbody>
</table>

(https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)
Non-viral mRNA delivery systems. Lipid-, polymer-, and emulsion-based delivery systems all use cationic groups to mediate condensation of the anionic RNA as well as delivery across the cell membrane.
Characteristics of DS’s LNP-mRNA

- DS original cationic lipid
- Efficient encapsulation of mRNA in nanoparticles, and efficient delivery of mRNA to targets
- Applicable to pandemic and other vaccines
Proposed mechanism of LNP-mediated subcellular mRNA delivery and process of antigen protein

1. LNP-mRNA uptake by the endosome
2. Acidification in the endosome that makes LNP cationic
3. LNP fusion to the endosomal membrane induced by electrostatic interaction
4. mRNA release to the cytoplasm
5. Translation to protein via the protein synthesis machinery
6. Proteasome-mediated or Endosome-mediated degradation and cell surface antigen (epitope) presentation

 Dynamin-mediated endocytosis

LNP-mRNA neutral in physiological condition

MHC class I

MHC class II

Endocytic compartment

Immuno-proteasome

Plasma membrane

Nucleus
Proposed immunogenic pathways of LNP-mRNA vaccine

**Protein production for CTL induction**
1. mRNA $\rightarrow$ protein (in DC)
2. mRNA $\rightarrow$ protein (in MΦ)

**Protein production for Ab response**
1. mRNA $\rightarrow$ protein (in Muscle)

**Lymph node**
1. Direct-priming
2. Cross-priming

CTL: cytotoxic T lymphocyte, DC: dendritic cells, MΦ: macrophage
Concept of LNP-mRNA vaccine (1/2)

【Pharmacological and safety profiles】

1. High-level, broad-spectrum antigen-specific immune responses are induced as compared with inactivated or recombinant protein antigens. In addition to antibody and helper T cell responses, cytotoxic T cells, which are necessary to eliminate intracellular pathogens, can be induced.

2. No interfering effect by existing immunity to vaccine formulations such as those observed in live attenuated vaccines and viral vectored vaccines confers stable boosting effects.

3. Due to high quality of antigen proteins produced in vivo, from the viewpoint of post-translational modification and conformation, induced immune responses are qualitatively superior to heterologously expressed antigen protein such as those produced in eggs, insects, or plants.

4. The risk of genetic injury in vaccines, such as carcinogenicity, immune deficiency, and transgenerational transmission, which poses a challenge to other types of genetic vaccines, is expected to be low.
【Quality and manufacturing profiles】

1. Lower risk in quality and manufacturing related to biologics, compared with live vaccines:
   • Non-pathogenic and relatively easy to handle in manufacturing
   • No requirement of bulky facilities for culture of cells or pathogens
   • The lack of in vivo replication ability makes it easier to determine dose

2. Once the platform has been established, development and manufacturing of a variety of LNP-mRNA vaccines can be streamlined
Significance of developing LNP-mRNA vaccines

- Original antigen design
- Feasible to supply vaccines containing novel antigens for breakthrough variants supposed to emerge in the future
- Having experiences in R&D for mRNA vaccine pipeline
- Expected to be superior in domestic development and distribution as compared with other leading mRNA vaccines developed in foreign countries
- To acquire capability of stable and emergency supply for vaccine preparedness and to become an essential infrastructure for emergency preparedness through collaboration with other organizations in the pharmaceutical industry
Structure of SARS-CoV-2 and vaccine modalities

Conventional Vaccines
- Whole Inactivated: Virus inactivated by chemicals or heat
- Live Attenuated: Wild type virus passed through several cell types until mutations accumulate that make it less able to cause disease
- Subunit Vaccine: Protein fragments from virus

Nucleic Acid Vaccines
- Synthetic Carrier
  - Synthetic mRNA encoding antigen of interest encapsulated in synthetic lipid or polymer carrier
- Viral Vectored
  - DNA encoding antigen of interest packaged in harmless virus (e.g., adenovirus)
- Electroporation
  - DNA encoding antigen of interest delivered by electroporation

Small envelope glycoprotein
Spike glycoprotein
Membrane glycoprotein
Hemagglutinin-acetyltransferase glycoprotein

(Vaccine 9:97 2021, https://doi.org/10.3390/vaccines9020097)
# Design of SARS-CoV-2 spike protein (S) antigen for DS-5670

<table>
<thead>
<tr>
<th></th>
<th>Full length (S-Full)</th>
<th>Receptor-binding domain (RBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of mRNA</td>
<td>• 4.1 kb</td>
<td>• 1.0 kb</td>
</tr>
</tbody>
</table>
| Proposed advantages          | • May contain additional neutralization epitopes and T cell epitopes other than those present in RBD | • Efficient and stable encapsulation of mRNA into LNP because ORF of RBD is shorter than that of S-Full  
• Lower risk of enhanced disease because potentially pathogenic epitopes are less as compared with S-Full (CELL 12060 https://doi.org/10.1016/j.cell.2021.05.032  

**ORF:** open reading frame
Superiority of RBD antigen to S-Full antigen

- Binding of RBD to ACE2 is cis-regulated by domains other than RBD, so-called ‘hip’, ‘knee’, and ‘ankle’.
- When using the S-Full of variants as vaccine antigen, mutations in ‘hip’, ‘knee’, and ‘ankle’ may affect the immunogenicity of RBD (may be evolutionally less immunogenic, enabling viral escape from host immune responses).
- In contrast, novel RBD antigens appropriate for emerging variants would be more simply designed and would be predictable.
By analyzing more than 650 serum samples from COVID-19 patients, it was suggested that more than 90% of neutralizing antibodies targeted RBD.

(The diagram shows the result of 21 samples, Cell 183:1024 2020)
Antibodies specific to N-terminal domain of spike protein and immune enhancement

Left: Characterization of monoclonal antibodies specific to different domain in S (NTD, RBD, or S2-TM), which were isolated from COVID-19 patients. The lowest panel shows effects of monoclonal antibodies on S-Full binding to ACE2.

Right: Enhanced and neutralizing antibody titers in serum obtained from COVID-19 patients.

(CELL 12060 https://doi.org/10.1016/j.cell.2021.05.032)
**Immunogenicity and protective efficacy of DS-5670 in cynomolgus monkeys (1/3)**

Results of research collaboration with the University of Tokyo and Shiga Medical University*

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**Diagram:**
- **Prime (i.m.):** 0 days
- **Boost (i.m.):** 7 days
- **Infection (2 × 10^7 TCID\(_{50}\)):** 21 days
- **Blood samples:** 0, 7, 14, 21 days

**Mock**
- **Swab samples:** Day after infection
- **Lung sample:** 28 days

**Graphs:**
- **Anti-RBD IgG titer in blood (10^9):**
  - Days: 0, 7, 14, 21, 28
  - 7 dpi

- **Neutralization activity in blood (2^11):**
  - Days: 0, 7, 14, 21, 28
  - 7 dpi

---

*This data was acquired in the “Fundamental Research on the Control of a Novel Coronavirus (2019-nCoV), which is an initiative supported by the Japan Agency for Medical Research and Development (AMED).

(Principal investigator: Prof. Yoshiro Kawaoka, Institute of Medical Sciences, The University of Tokyo)
Immunogenicity and protective efficacy of DS-5670 in cynomolgus monkeys (2/3)
Results of research collaboration with the University of Tokyo and Shiga Medical University*

*This data was acquired in the "Fundamental Research on the Control of a Novel Coronavirus (2019-nCoV), which is an initiative supported by the Japan Agency for Medical Research and Development (AMED).
(Principal investigator: Prof. Yoshiro Kawaoka, Institute of Medical Sciences, The University of Tokyo)
Immunogenicity and protective efficacy of DS-5670 in cynomolgus monkeys (3/3)

Results of research collaboration with the University of Tokyo and Shiga Medical University*

*This data was acquired in the "Fundamental Research on the Control of a Novel Coronavirus (2019-nCoV), which is an initiative supported by the Japan Agency for Medical Research and Development (AMED). (Principal investigator: Prof. Yoshiro Kawaoka, Institute of Medical Sciences, The University of Tokyo

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Prime (i.m.) → Boost (i.m.) → Infection ($2 \times 10^7$ TCID$_{50}$) → 28 days → Day after infection

Swab Swab Swab Swab Swab

Lung

TCID$_{50}$ in swab samples after viral challenge

Nasal cavity

Oral cavity

Trachea

Bronchus

Mock

DS-5670

log TCID$_{50}$/mL

0 1 2 3 4 5

0 1 2 3 4 5

0 1 2 3 4 5

0 1 2 3 4 5

d.p.i

d.p.i

d.p.i

d.p.i

0 1 3 5 7
Cross-neutralizing activity against recently emerged variants

- Cynomolgus monkey
- 50 μg/body of DS-5670 by mRNA conversion
- Dosed in brachial deltoid muscle q2w, total 3 times (4 monkeys/group)
- Measured neutralizing activity using plasma collected 2 weeks after the third dose (AMED Kawaoka group)

<table>
<thead>
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<th>Monkey ID</th>
<th>D614G</th>
<th>α</th>
<th>γ</th>
<th>β</th>
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<td>640</td>
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**SARS-CoV-2 variant**

- D614G
- α  N501Y
- γ  K417T/E484K/N501Y
- β  K417N/E484K/N501Y
- δ  L452R/T478K
- κ  L452R/E484Q

*This data was acquired in the AMED’s drug discovery support program “Development of a Vaccine for COVID-19 Vaccines”.

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*Variant Mutation in RBD*

- α  N501Y
- γ  K417T/E484K/N501Y
- β  K417N/E484K/N501Y
- δ  L452R/T478K
- κ  L452R/E484Q
Selected to be a provider for the MHLW’s “Emergent Initiative to Build Production Capacity for COVID-19 Vaccines*1 (First Round)”

Selected to be a company for the AMED’s drug discovery support program “Development of a Vaccine for COVID-19 Vaccines*2 (Second Round)”

Initiated **Ph1/2 study** in March 2021 and data expected around autumn 2021. Currently evaluating the safety, immunogenicity, and recommended dose.

To initiate **active-controlled, non-inferiority confirmatory study** this year, in which several thousand subjects will be enrolled

**BLA and commercialization expected in CY2022** when all regulatory requirements are satisfied

A clinical trial for booster vaccination also being planned and considered

The overall development plan and designs of further studies being continuously discussed with the Health Authority

*1 The project aims to swiftly develop an actual (large-scale) production system for biologics, including vaccines, in order to ensure that the vaccines necessary for the prevention of the spread and severity of unexpected epidemics, including COVID-19, are produced as soon as possible, and that their supply is secured for the Japanese people.

*2 The project aims to support the development of a vaccine against COVID-19, for which R&D is already underway, and aims to ensure the early commercialization of safe and effective vaccines.