MF59-adjuvanted SARS-CoV-2 Vaccine

Development Update

Presentation to the European Commission

5.1.2e
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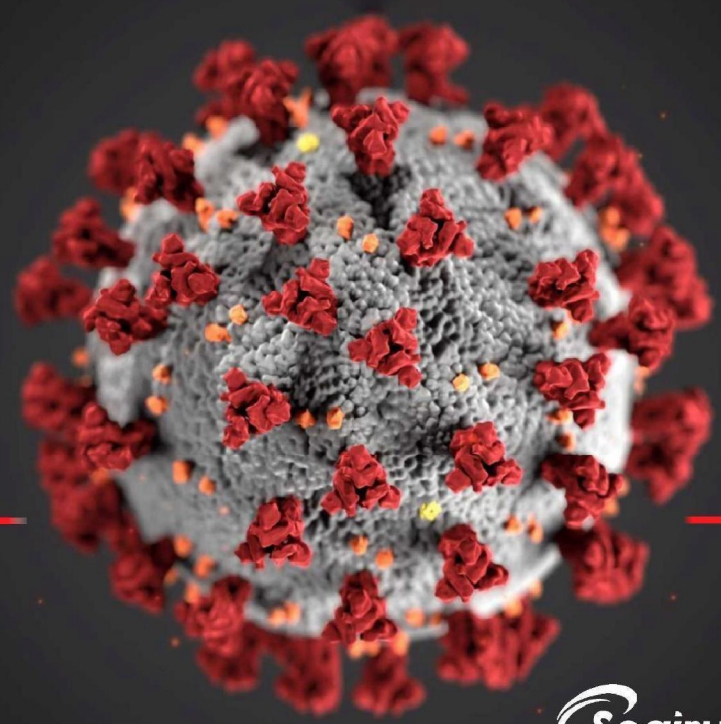
August 11, 2020 – Updated August 25, 2020



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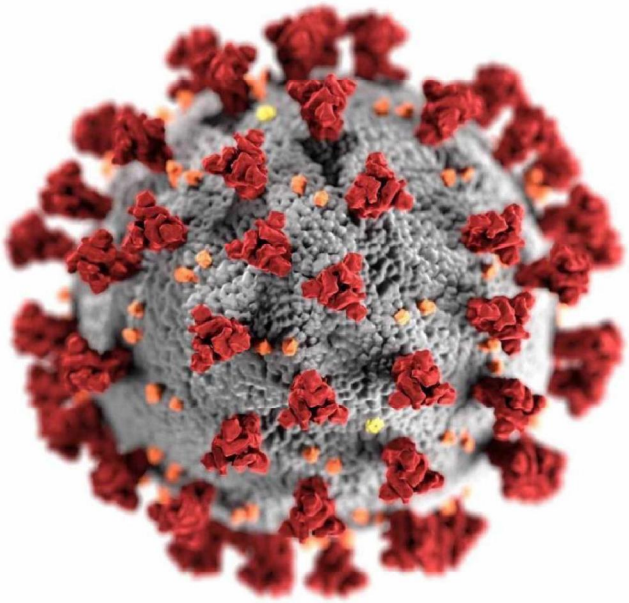

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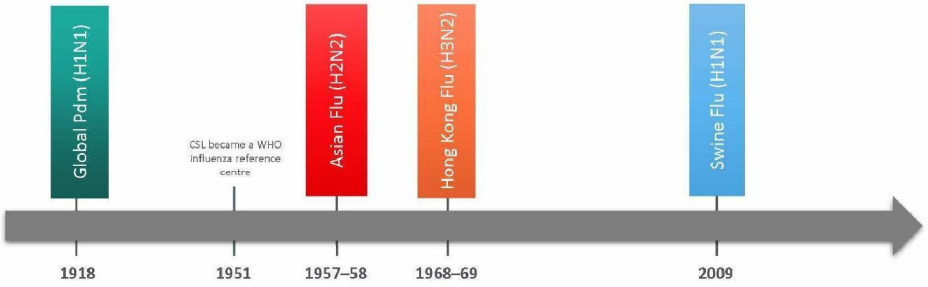
INTRODUCTION

CSL: A LONG-STANDING HERITAGE IN PUBLIC HEALTH

- Seqirus is part of the CSL Group, a global biotech leader in the development and large-scale manufacture of vaccines, plasma therapeutics, and recombinant proteins
- CSL was founded by the Australian Government over 100 years ago to protect against public health threats, including the 1918 Influenza pandemic
- Seqirus continues to work on the front line of influenza protection, providing innovative seasonal vaccines and pandemic preparedness solutions to public health partners around the world
- In March 2019, the EU Commission and 14 member states have partnered with Seqirus on pandemic influenza preparedness through the Joint Procurement framework



5.1.2e

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Image: Seqirus archives.

INTRODUCTION

CSL: A GLOBAL SPECIALTY BIOTHERAPEUTICS COMPANY

DEVELOPMENT AND LARGE-SCALE MANUFACTURE OF VACCINES, PLASMA THERAPEUTICS, AND RECOMBINANT PROTEINS

60+ Countries
Of operation around the world

US$ **8.5+** Billion
In annual revenue

US$ **3.3+** Billion
In R&D investments in past 5 years advances exciting pipeline

8
Manufacturing sites

- Australia (2)
- China (1)
- Germany (1)
- Switzerland (1)
- United Kingdom (1)
- United States (1)

26,000+
Employees around the world

1700+
R&D employees

257+
Plasma collection centres across Europe and North America

Delivering **innovative** biotherapies that **save lives** and enable those with **life-threatening conditions** to live full lives

Applying **established** experience in fighting **public health emergencies** to the battle against **COVID-19**

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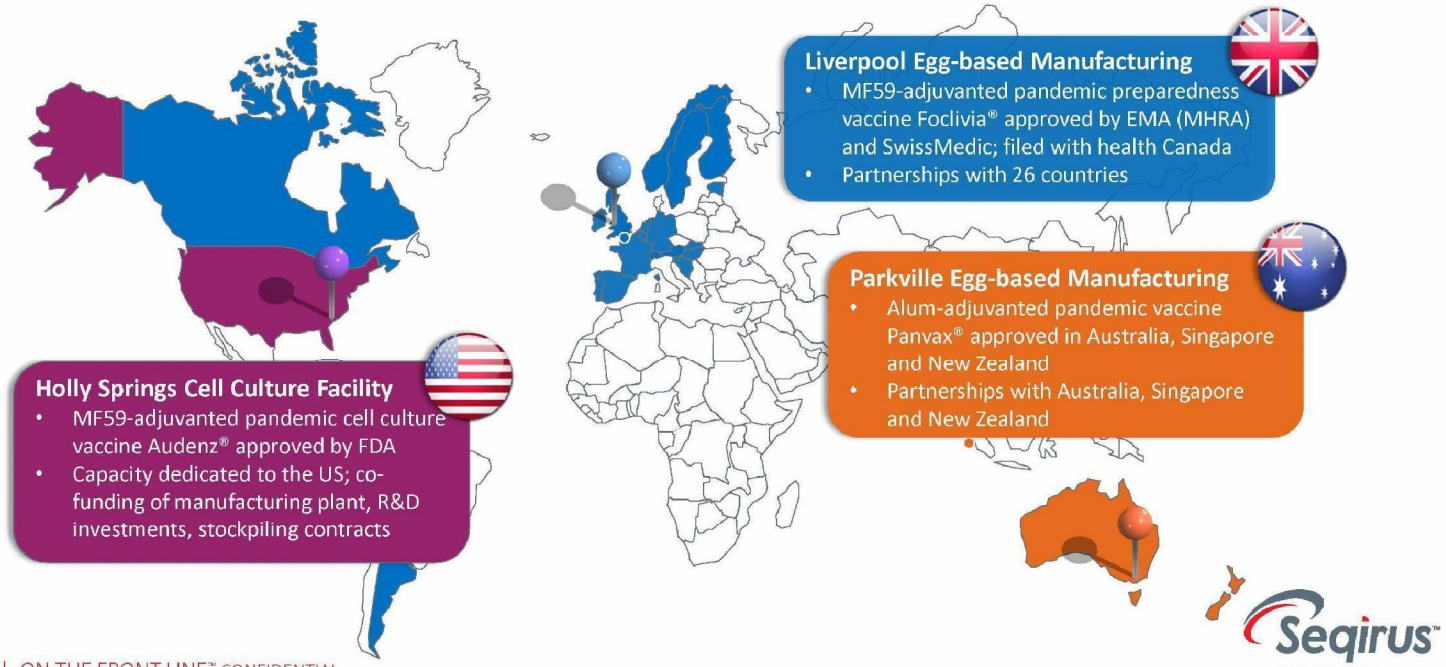
Source: Seqirus data on file.
COVID-19, coronavirus disease; R&D, research and development.

INTRODUCTION

SEQIRUS IS A GLOBAL LEADER IN PANDEMIC INFLUENZA PREPAREDNESS

APPROVED MF59-ADJUVANTED VACCINES & INDUSTRIALIZED CELL CULTURE TECHNOLOGY



Holly Springs Cell Culture Facility
- MF59-adjuvanted pandemic cell culture vaccine Audenz® approved by FDA
- Capacity dedicated to the US; co-funding of manufacturing plant, R&D investments, stockpiling contracts

Liverpool Egg-based Manufacturing
- MF59-adjuvanted pandemic preparedness vaccine Foclivia® approved by EMA (MHRA) and SwissMedic; filed with health Canada
- Partnerships with 26 countries

Parkville Egg-based Manufacturing
- Alum-adjuvanted pandemic vaccine Panvax® approved in Australia, Singapore and New Zealand
- Partnerships with Australia, Singapore and New Zealand

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INTRODUCTION

CSL: OUR GLOBAL ROLE IN COMBATTING COVID-19

PURSUING SEVERAL PROJECTS CONSIDERED SCIENTIFICALLY SOUND AND FITTING OUR CAPABILITIES

SARS-CoV-2 vaccine
- Partnership with the Coalition for Epidemic Preparedness Innovations (CEPI) and The University of Queensland (UQ) to accelerate the development, manufacture, and distribution of a COVID-19 vaccine candidate

Evaluation of MF59® to support third party vaccine R&D
- Well-established in pandemic and adjuvanted seasonal influenza vaccine for the over-65 age group, MF59® can help improve immune response and reduce the amount of antigen needed for each vaccine dose

Anti-SARS-CoV-2 polyclonal hyperimmune immunoglobulin
- Development of an anti-SARS-CoV-2 plasma product for the Australian market with the potential to treat people with serious complications of COVID-19
- Unprecedented industry partnership in the CoVIg-19 Plasma Alliance leveraging leading-edge expertise and work across companies; working with the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health to test the safety, tolerability, and efficacy of the hyperimmune therapy

High-potency human polyclonal antibodies immunotherapy
- Partnership with SAB Biotherapeutics to advance a novel immunotherapy targeting COVID-19; produced without the need for blood plasma donations

Experimental approaches on monoclonal antibodies as treatment for severe respiratory distress

Support of various governments with expertise, technologies, equipment, and materials

Seqirus remains focused on the production of seasonal influenza vaccines for the upcoming season, the importance of which is very much underscored by the COVID-19 pandemic

Source: CSL Behring. CSL Behring's Global Role in Battling COVID-19. 2020. Available at: https://www.cslbehring.com/newsroom/2020/covid-19-cslb-facts. Accessed: July 6, 2020.
COVID-19, coronavirus disease; R&D, research and development; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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INTRODUCTION

CSL IS PARTNERING WITH THE UNIVERSITY OF QUEENSLAND AND CEPI TO DEVELOP A SARS-COV-2 VACCINE CANDIDATE

The University of Queensland (UQ) has initiated the development of a recombinant subunit vaccine for SARS-CoV-2 using "molecular clamp" technology

- Funding received from CEPI, the Queensland State, and Australian Federal Government to develop

CSL has entered into a partnership with UQ and Coalition for Epidemic Preparedness Innovations (CEPI) to accelerate development, manufacture, and distribution of the vaccine candidate

- UQ will lead the Phase 1 clinical study
- CSL/Seqirus will lead the later stages of clinical development, and will be responsible for regulatory submissions, process development, and manufacturing of the vaccine

CEPI and CSL/Seqirus will share the cost of the program and the doses manufactured

- CEPI's vaccine allocation will be distributed through the COVID-19 Vaccine Global Access Facility, in which CEPI works in partnership with GAVI and the World Health Organization
- CSL's allocation will supply doses to governments having entered into agreements for access
- CSL has granted CEPI a first right of refusal to any surplus doses, to be distributed through the COVID-19 Vaccine Global Access Facility

Source: CSL. The University of Queensland, CEPI and CSL partner to advance development and manufacture of COVID-19 vaccine candidate. 2020. Available at: https://www.csl.com/news/2020/20200605-uq-cepi-and-csl-partner-for-covid-19-vaccine-candidate. Accessed: July 15, 2020.
COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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CSL/SEQIRUS: BRINGING CRITICAL CAPABILITIES TO THE PROGRAM

Long-standing experience in research and clinical development of innovative vaccines

Leading influenza vaccine and recombinant protein manufacturer with deep knowledge of process and formulation development and scale-up

Proven MF59® adjuvant system with 20-year history of use in influenza vaccine and unparalleled safety database

Internal manufacturing capacity to supply clinical trials and initial commercial doses

- Antigen manufacturing in CHO cells (Parkville and Broadmeadows, Australia; Marburg, Germany)
- Manufacturing of adjuvant system
- Vaccine formulation
- Filling and finishing of multi-dose vials

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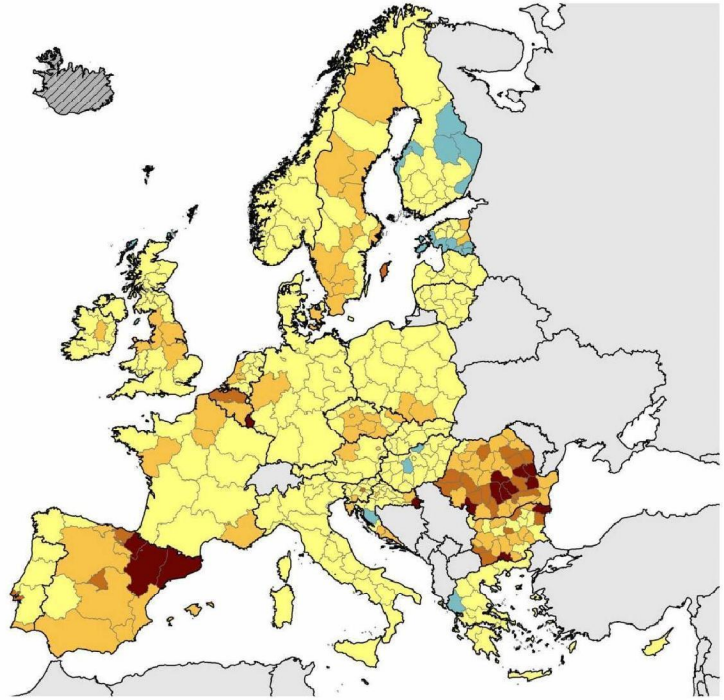
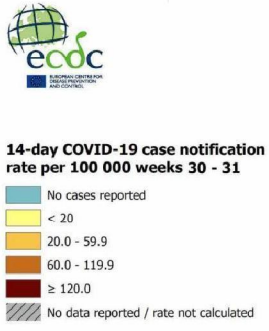
 CHO, Chinese hamster ovary.

INTRODUCTION

SARS-COV2 EPIDEMIOLOGY





Source: COVID-19 situation update for the EU/EEA and the UK, as of 8 August 2020 (2020). Available at: https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea (Accessed: 8 August 2020).

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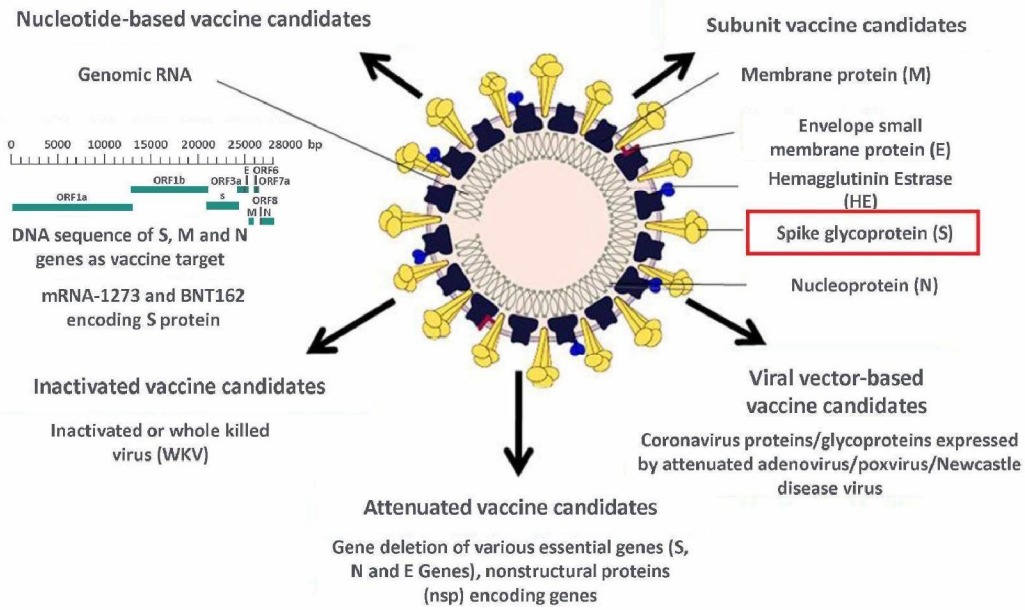
DEVELOPMENT ACTIVITIES

SARS-CoV-2: VACCINE CANDIDATES



Pandey SC et al. *Life Sciences* 2020;256:117956.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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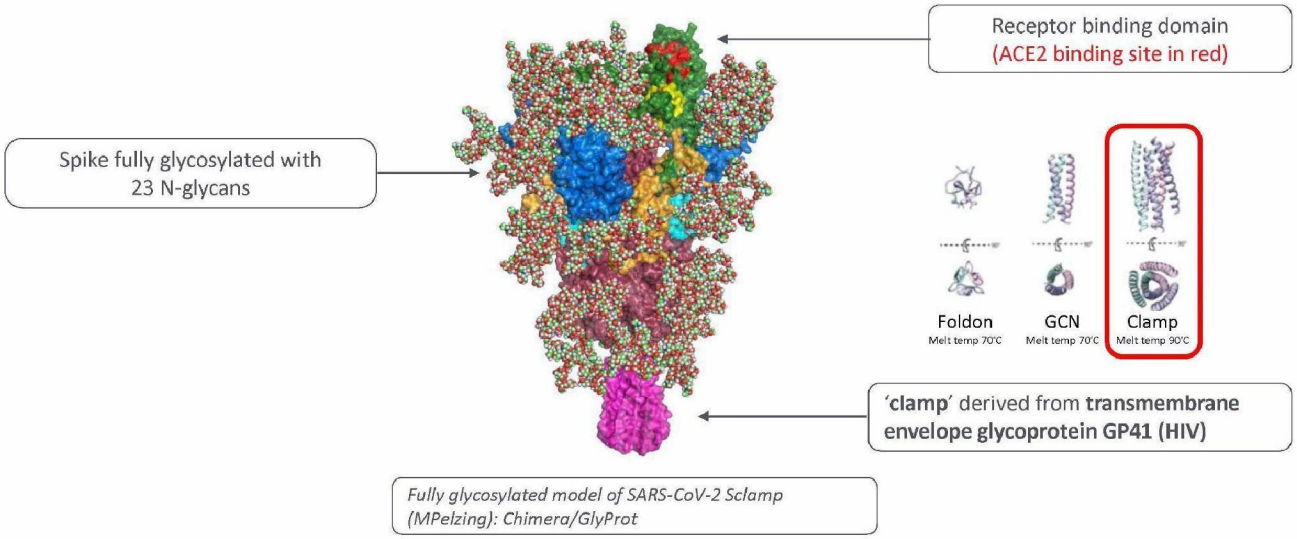
DEVELOPMENT ACTIVITIES

SARS-CoV-2: S-CLAMP ANTIGEN



Molecular clamp aims to stabilise spike protein in trimer form

ACE, angiotensin-converting enzyme; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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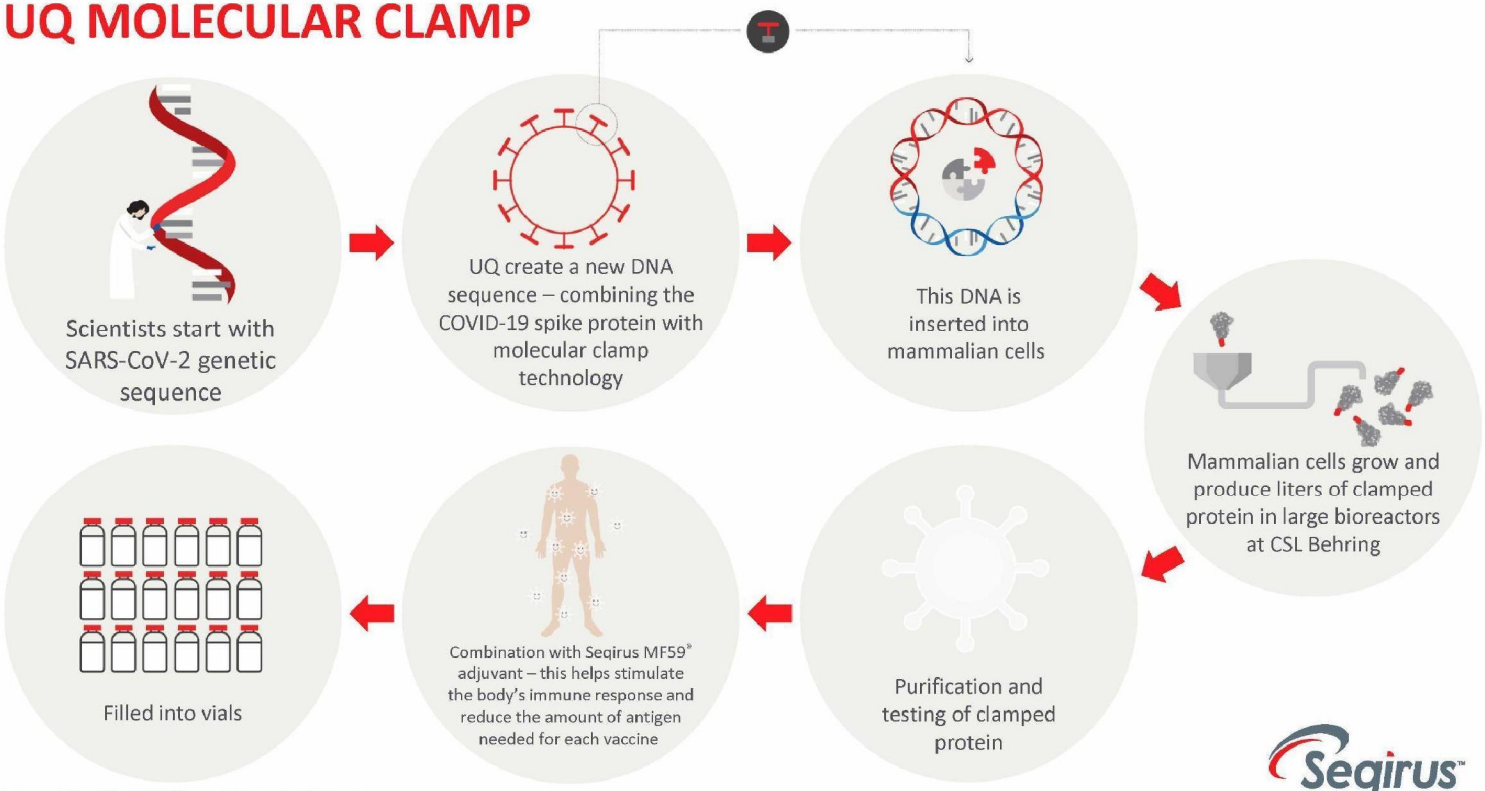
DEVELOPMENT ACTIVITIES

UQ MOLECULAR CLAMP



 SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UQ, The University of Queensland.

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DEVELOPMENT ACTIVITIES

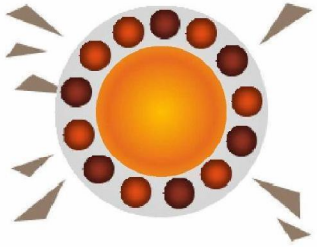
MF59®-ADJUVANTED INFLUENZA VACCINES DEMONSTRATED FAVORABLE EFFICACY AND SAFETY PROFILES IN ALL POPULATIONS

Antigen Sparing

- H5N1 and H1N1 clinical trials showed 1/4 to 1/12 of antigen sufficient to meet approval criteria compared with unadjuvanted vaccines†,[1–3]

Safety Profile

- 20 years of seasonal, pandemic, and pre-pandemic use[1,2]
- >150 million doses distributed[1,2,10]
- Data from more than 100,000 subjects in clinical and observational trials[11]
- Controlled trial data in >5000 children, 18,000 adults, and 15,000 elderly[11]
- No safety signals in clinical trials or pharmacovigilance databases[11]



Cross Protection

- MF59® expands antibody repertoire[4]
- Primed subjects generate cross-reactive antibodies[5,6]

Higher Immunogenicity

- MF59®-primed subjects have higher antibody responses[7,8]
- In an animal model MF59®-adjuvanted vaccine lead to absence of H1N1 in lungs and nose[9]

†Unadjuvanted H5N1 vaccine requires 90 µg HA.

[1]Keitel W et al. *Vaccine*. 2010;28:840–848; [2]Vesikari T et al. *Vaccine*. 2012;30:1388–1396; [3]Frey S et al. *Vaccine*. 2003;21:4234–4237; [4]Seqirus, pharmacovigilance data on file; [5]Podda A, Del Giudice G. *Exp Rev Vaccines*. 2003;2:197–204; [6]O'Hagan DT. *Exp Rev Vaccines*. 2007;6:699–710; [7]Galli G et al. *Proc Natl Acad Sci USA*. 2009;106:7962–7967; [8]Del Giudice G et al. *Sci Transl Med*. 2009;1:12re1; [9]Khurna S et al. *Sci Transl Med*. 2010;2:15ra5; [10]Black S. *Vaccine*. 2015;33:B3–5; [11]Panatto D. et al *Influenza Other Respir Viruses*. 2020;14:61–66.

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DEVELOPMENT ACTIVITIES

COVID-19 VACCINE: DEVELOPMENT

- COVID-19 vaccine is a recombinant subunit vaccine manufactured using a stably transfected CHO cell line
- COVID-19 vaccine is highly purified and well characterized
- MF59® adjuvant has a comprehensive safety profile
- Medicinal products developed by biotechnological processes, such as recombinant DNA technology, fall within the mandatory scope of the Annex of Regulation (EC) No 726/2004. Applicants are obliged to use the centralized authorization procedure

 CHO, Chinese hamster ovary; COVID-19, coronavirus disease; DNA, deoxyribonucleic acid; EMA, European Medicines Agency.

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DEVELOPMENT ACTIVITIES

THE DEVELOPMENT ACTIVITIES ARE ADVANCING TO PLAN

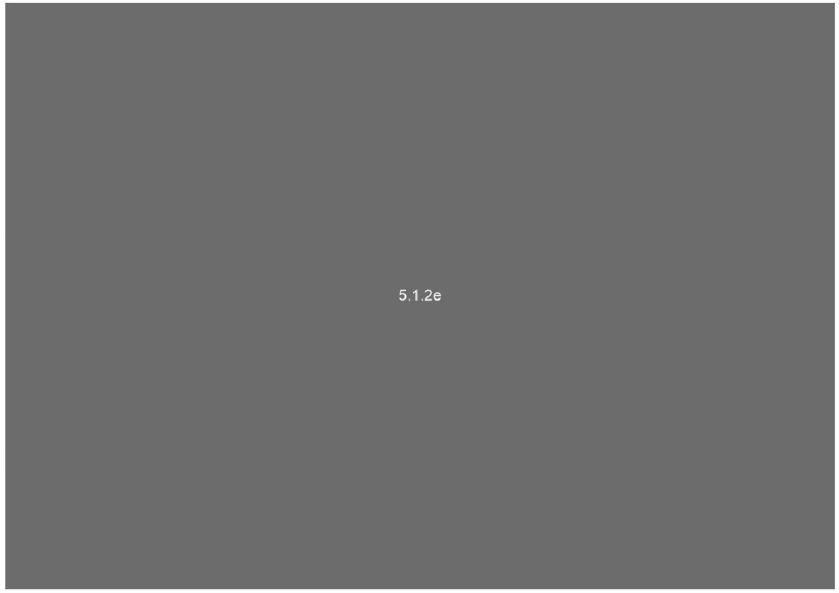
FIRST SUBJECT DOSED IN PHASE 1 STUDY ON JULY 13

Phase 1 Study Design

- Safety, reactogenicity, and immunogenicity
- Adults aged 18–55 years
- Dose-escalation, 3 active dose groups
- 1- or 2-dose groups
- First low- and medium dose cohort (n=32) dosed; high dose started

Phase 1 Study Outcomes

- Reactogenicity
- Safety (SAEs/AESIs)
- Humoral and CMI responses



Source: The University of Queensland. First dose. 2020. Available at: https://stories.uq.edu.au/news/2020/first-human-trial-of-UQs-COVID-19-vaccine/index.html. Accessed: July 15, 2020.

AESI, adverse event of special interest; CMI, cell-mediated immunity; SAE, serious adverse event.

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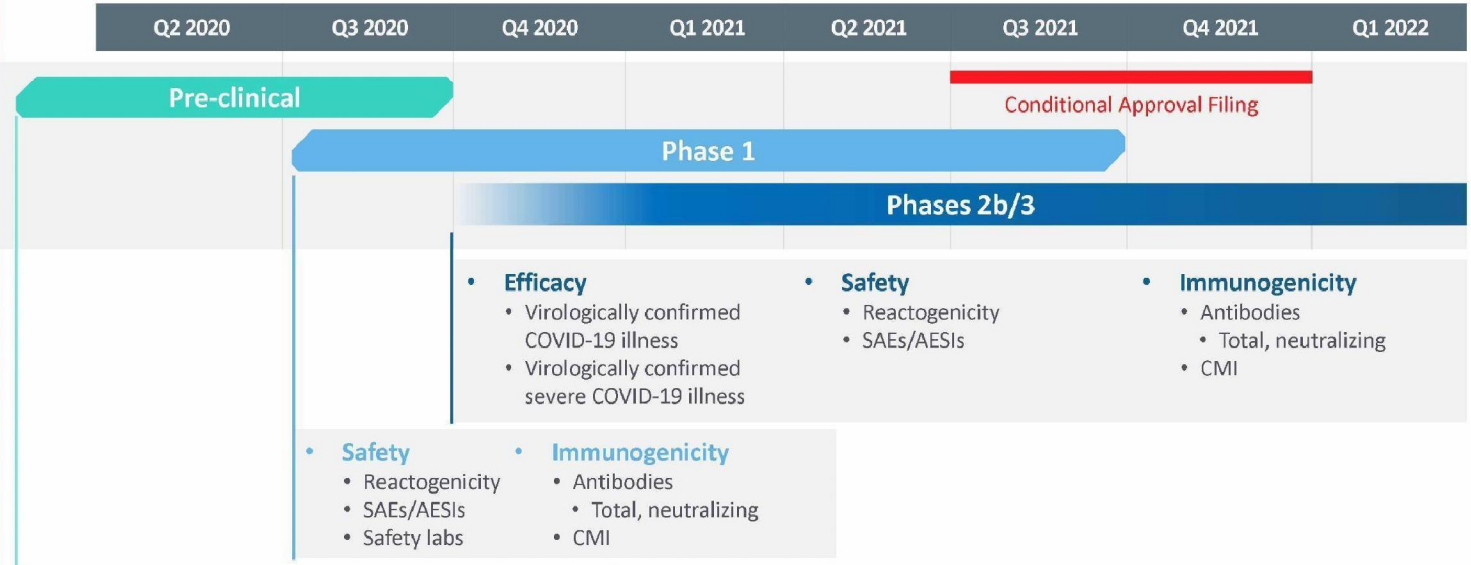
DEVELOPMENT ACTIVITIES

TIMELINES AND ENDPOINTS



Pre-clinical

- Mouse humoral and CMI immunogenicity studies
- Animal challenge studies
- Toxicity studies

AESI, adverse event of special interest; CMI, cell-mediated immunity; COVID-19, coronavirus disease; Q, quarter; SAE, serious adverse event.

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VACCINE ACCESS

STAGED PAYMENTS BASED UPON DEVELOPMENT SUCCESS

A risk-sharing approach to payment:

- A vaccine in development must pass a number of critical "stage gates" to get to the next stage of development – usually related to clinical success or manufacturing scale-up
- Later stages of development – Phase 3 trials and industrial scale-up – are the most expensive
- Seqirus proposes a number of staged payments, coinciding with stage-gate successes
- The proportion of the final cost payable at each stage will be equivalent to the proportion of the overall development investment made by Seqirus

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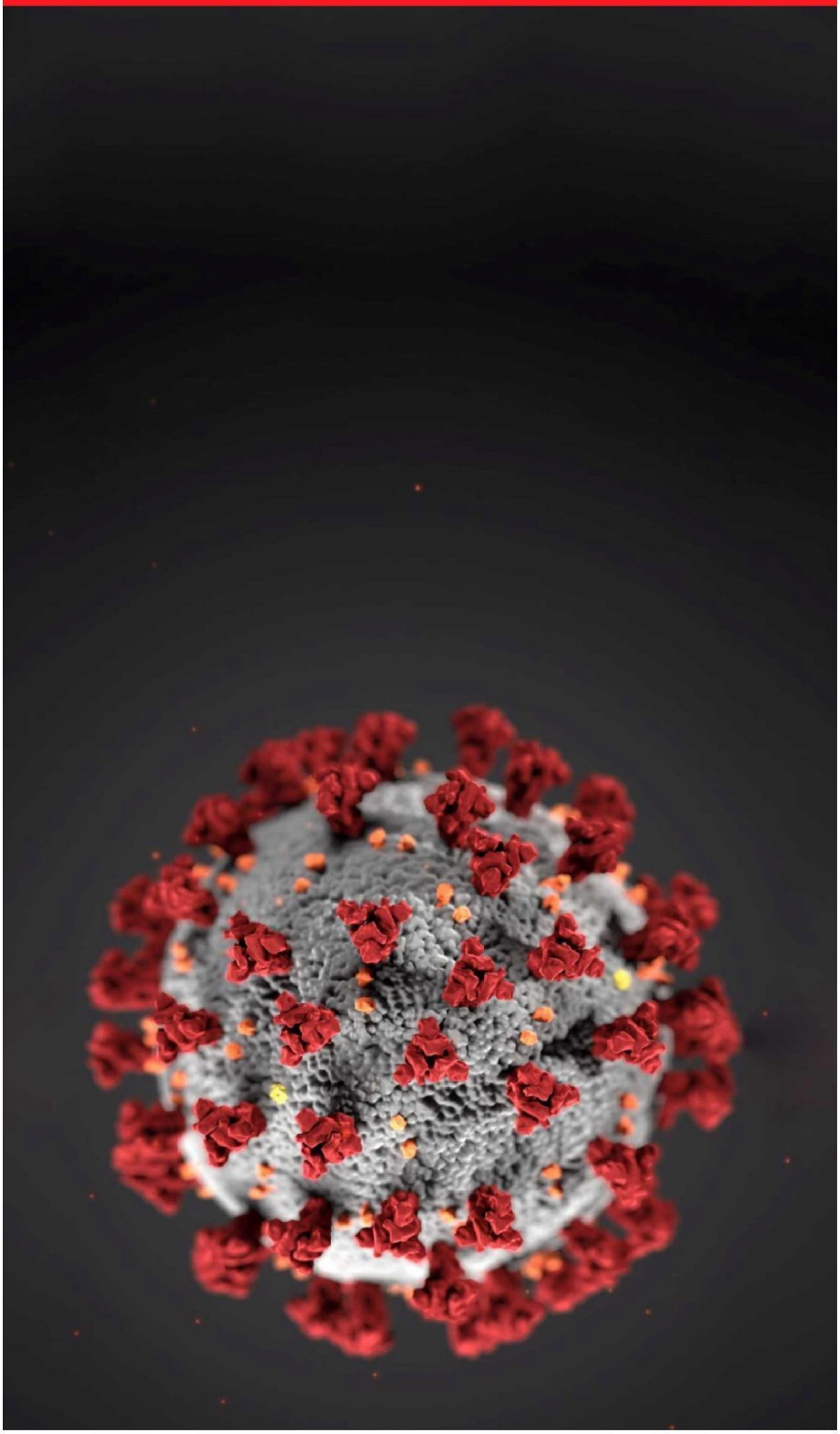
SUPPLEMENTAL DATA



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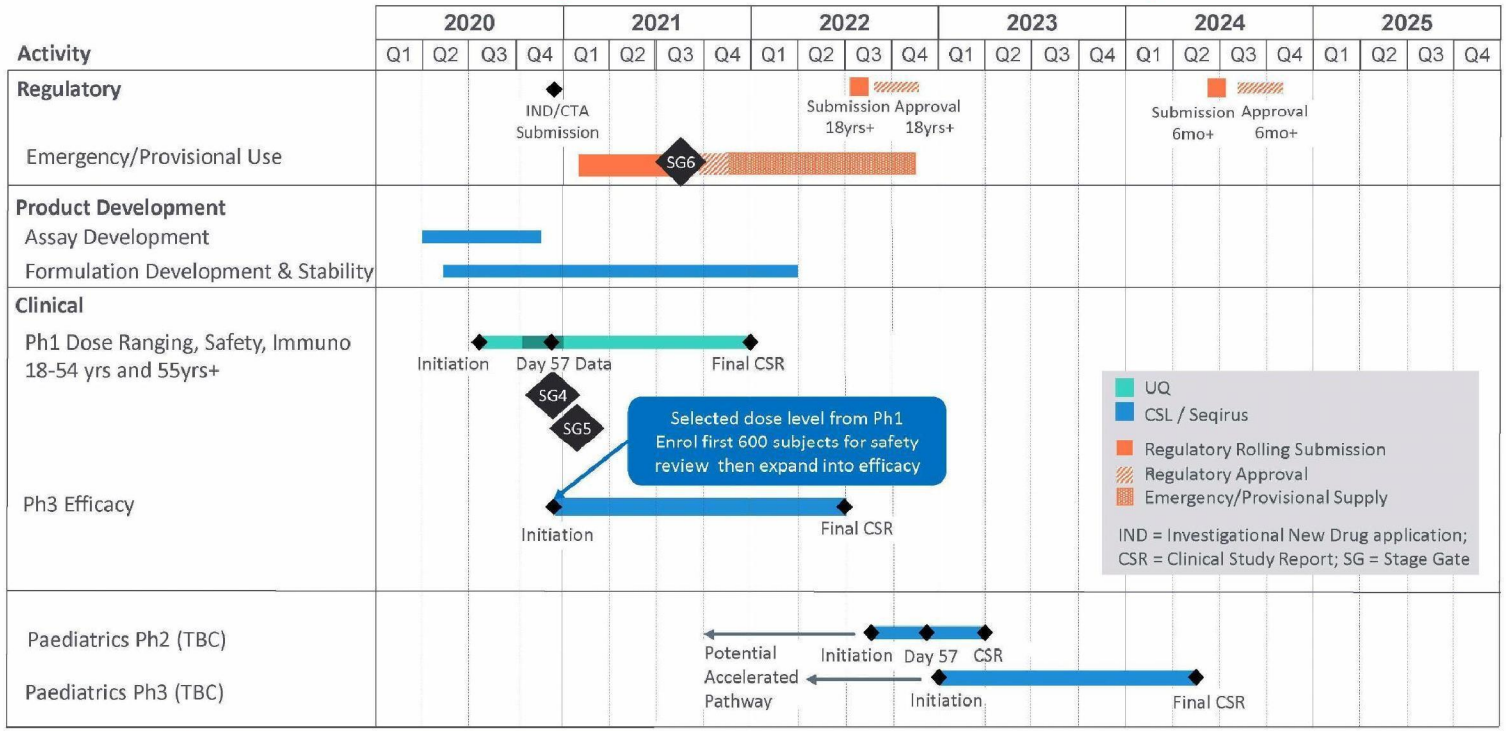
DEVELOPMENT ACTIVITIES

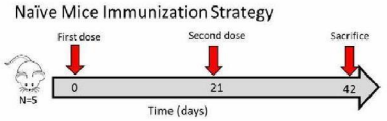
PROGRAM MILESTONES (SUBJECT TO FINALIZATION)



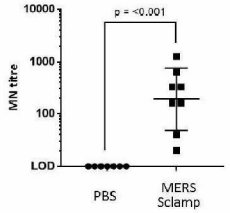
DEVELOPMENT ACTIVITIES

MERS S-CLAMP PROOF OF PRINCIPLE
HUMORAL AND CELLULAR RESPONSE SUMMARY

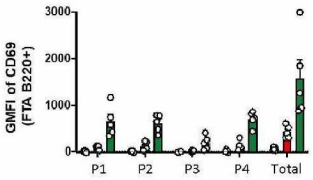
Mice received two doses of MERS Sclamp vaccine ± MF59 adjuvant • Immune responses assessed 3 weeks after final dose



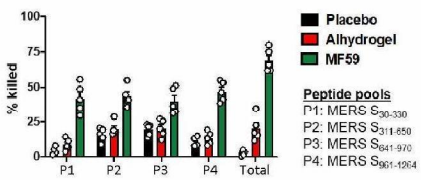
Live virus neutralization



T-helper cell response



Cytotoxic T-cell response



Inclusion of MF59

Stimulates T helper and cytotoxic T cell responses that span four different peptide pools

Outperforms placebo or vaccine adjuvanted with alhydrogel

Robust and directed humoral and cell-mediated immune responses in MERS model

MF59 stimulates T helper and cytotoxic T cell responses

FTA, fluorescent target array; GMFI, geometric mean fluorescence intensity; MERS, Middle East respiratory syndrome-related coronavirus; PBS, phosphate-buffered saline.

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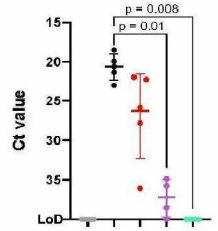
DEVELOPMENT ACTIVITIES

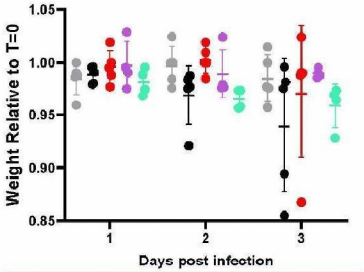
MERS S-CLAMP PROOF OF PRINCIPLE
MOUSE CHALLENGE PROTECTION STUDY

hDPP4 transgenic mouse model ● Formalin-treated MERS-CoV emulates enhanced disease ● Challenge at 3 weeks after final vaccine dose

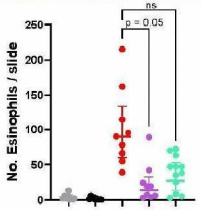
Lung Viral Load



Body Weight



Lung Eosinophil Count



Histopathology Scoring

Group	Bronchioles	Blood Vessels	Alveoli
Healthy Control	+	+	++
Placebo	+	+	+
Formalin Treated MERS-CoV	+++	+++	+++
1 mcg MERS Sclamp + MF59	++	+	++
5 mcg MERS Sclamp + MF59	++	++	++

● Healthy control ● Placebo ● Formalin treated virus ● 1ug MERS Sclamp + MF59 ● 5ug MERS Sclamp + MF59

MF59-adjuvanted Sclamp vaccine associated with:

No weight loss

No, or minimal, viral load in the lung

Minimal lung infiltration with eosinophils

Favorable histopathology score

Lung viral load below level of detection for 5µg dose of MERS antigen with MF59.

Minimal eosinophil infiltration in lungs

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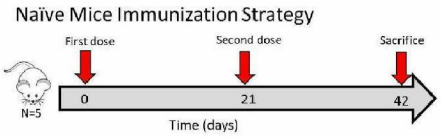
 Ct, cycle threshold; hDPP4, human dipeptidyl peptidase 4; MERS-CoV, Middle East respiratory syndrome-related coronavirus.

DEVELOPMENT ACTIVITIES

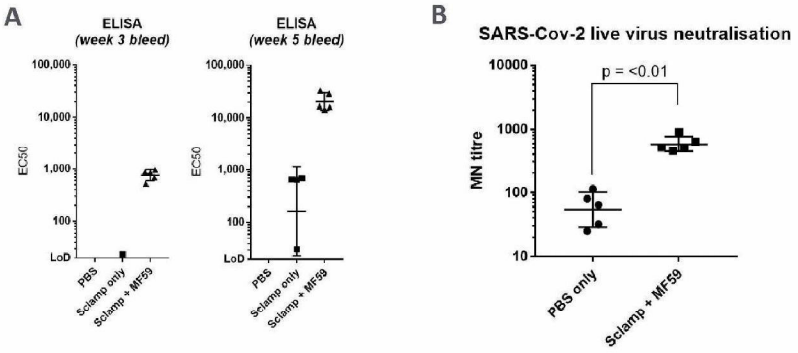
SARS-CoV-2 IMMUNOGENICITY STUDY IN MICE
HUMORAL RESPONSES

Mice received two doses of SARS-CoV-2 Sclamp vaccine ± MF59 adjuvant ● Immune responses assessed 3 and 5 weeks after first dose



50 µL intramuscular injection
5 µg SARS-CoV-2 Sclamp + 25 µL MF59

Humoral Immune Response



Strong antibody response after second dose (with MF59) in SARS-CoV2 model

Antibodies prevent virus from infecting host cells (neutralization)

ELISA, enzyme-linked immunosorbent assay; MN, microneutralization; PBS, phosphate-buffered saline; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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DEVELOPMENT ACTIVITIES

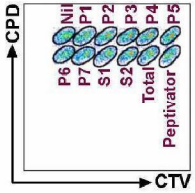
SARS-CoV-2 IMMUNOGENICITY STUDY IN MICE
FLUORESCENT TARGET ARRAY ANALYSIS (FTA) - **METHODOLOGY**

2 × i.m. doses given at 3-weekly intervals

19 days after the 2nd dose

15 h

Flow cytometry analysis
* % killed (CTL response)
* CD69 expression on FTA B220+ cells (T cell help)



Vaccination Groups
PBS dosed (placebo)
SARS-CoV-2 Sclamp (Ag) only (5 µg/dose)
Ag (5 µg/dose) + Alhydrogel (50 µg/dose)
Ag (5 µg/dose) + MF59 (50% v/v)

Transfer 2 × 10^6 naive FTA cells/population pulsed with each peptide pool spanning SARS-CoV-2 S_{1-1226}

Ag, antigen; CPD, cell proliferation dye; CTL, cytotoxic T lymphocyte; CTV, cell trace violet; FTA, fluorescent target array; ICS, intracellular cytokine staining; i.m., intramuscular; PBS, phosphate-buffered saline; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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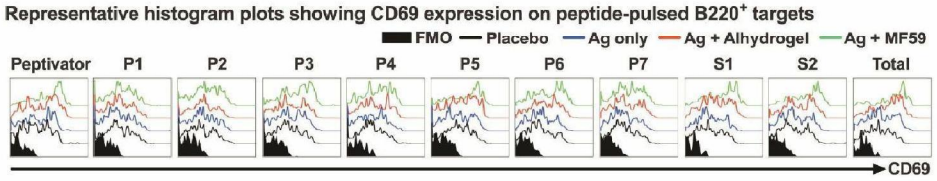
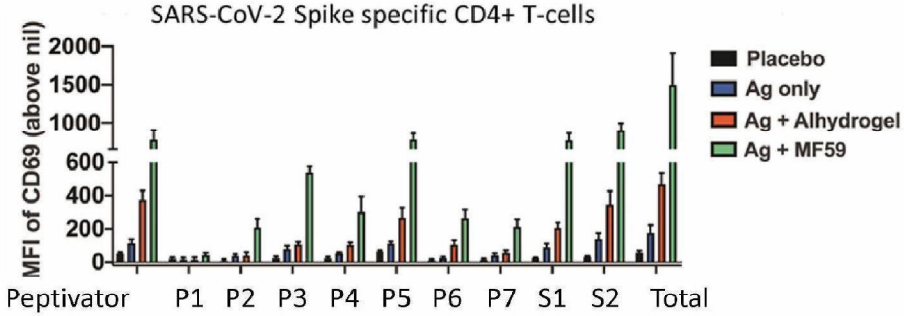
DEVELOPMENT ACTIVITIES

SARS-CoV-2 FTA ANALYSIS
SPIKE-SPECIFIC T HELPER CELL RESPONSES





Spike -specific T helper responses higher with MF59 adjuvant than antigen alone

Ag, antigen; CPD, cell proliferation dye; CTV, cell trace violet; FSC-H, forward scatter height; FTA, fluorescent target array; MFI, mean fluorescence intensity; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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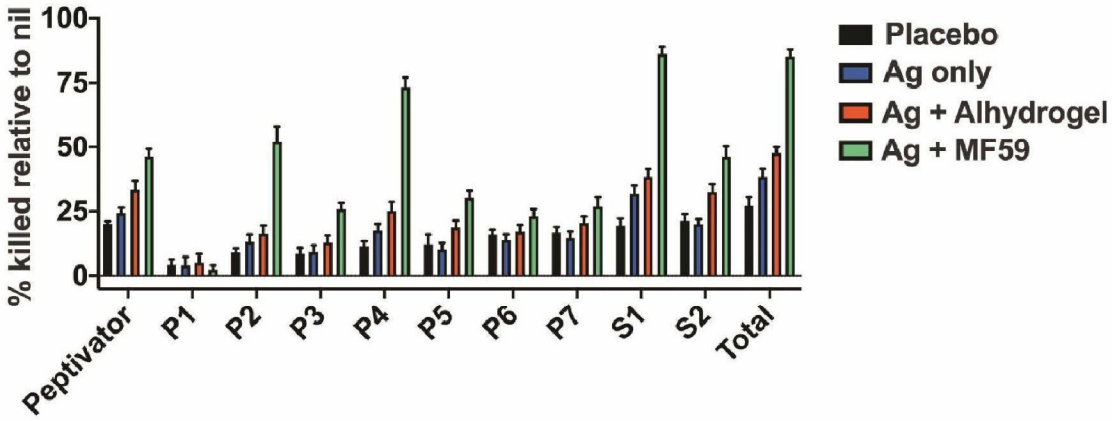
DEVELOPMENT ACTIVITIES

SARS-CoV-2 IMMUNOGENICITY STUDY IN MICE

FTA ANALYSIS OF S-SPECIFIC CYTOTOXIC T CELL RESPONSE

Summary (mean (n = 5) + SEM) analysis of the CTL response



Spike-specific cytotoxic T cell response higher with MF59 adjuvant than with antigen alone

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Ag, antigen; CTL, cytotoxic T lymphocyte; FTA, fluorescent target array; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEM, standard error of the mean.

DEVELOPMENT ACTIVITIES

SARS-CoV-2 IMMUNOGENICITY STUDY IN MICE

INTRACELLULAR CYTOKINE STAINING (ICS) - **METHODOLOGY**

24 days after the 2nd dose →

Stimulate splenocytes with 18mer peptides spanning SARS-CoV-2 S_{1-1226} →

Analyze the expression of cytokines and cytotoxic molecules produced by S-specific $CD4^+$ and $CD8^+$ T cells

2 × i.m. doses given at 2-weekly intervals

Vaccination Groups

PBS dosed (placebo)
SARS-CoV-2 Sclamp (Ag) only (5 µg/dose)
Ag (5 µg/dose) + Alhydrogel (50 µg/dose)
Ag (5 µg/dose) + MF59 (50% v/v)

Ag, antigen; CPD, cell proliferation dye; CTL, cytotoxic T lymphocyte; CTV, cell trace violet; FTA, fluorescent target array; ICS, intracellular cytokine staining; i.m., intramuscular; PBS, phosphate-buffered saline; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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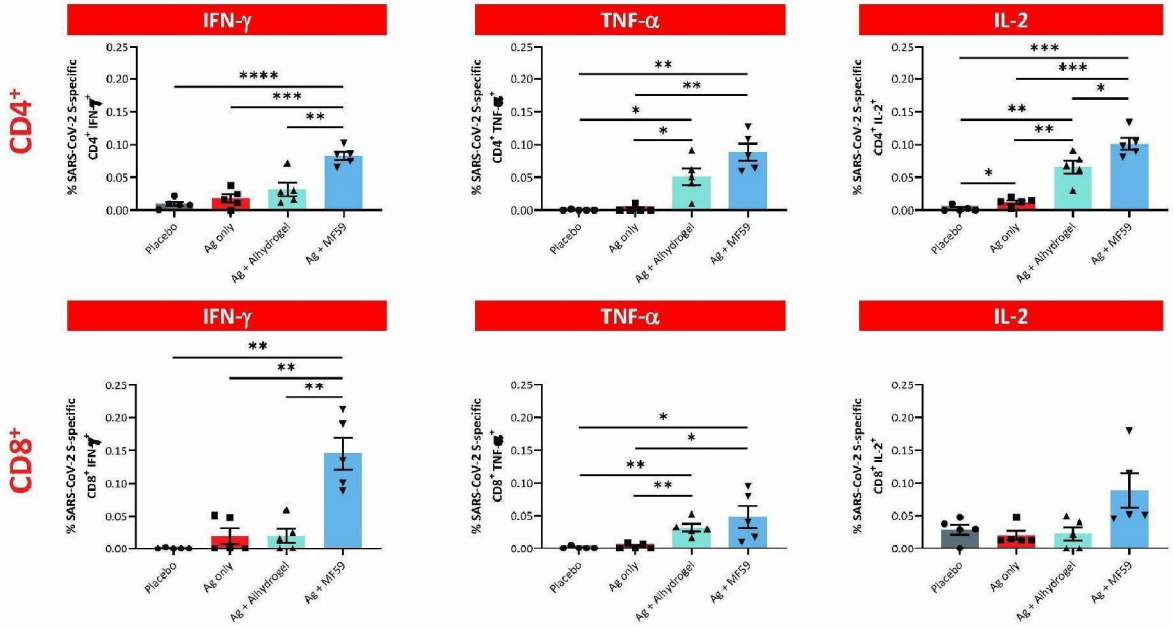
DEVELOPMENT ACTIVITIES

MF59 STIMULATES EXPRESSION OF Th1-TYPE CYTOKINES CYTOTOXIC AND HELPER T CELLS



Significant Th1 immune response (Th1: IFN-gamma, TNF-alpha, IL-2)

Potential mitigation of risk of enhanced disease

*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. Each bar represents stimulated minus non-stimulated value.
Ag, antigen; IFN-γ, interferon gamma; IL-2, interleukin-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor alpha.

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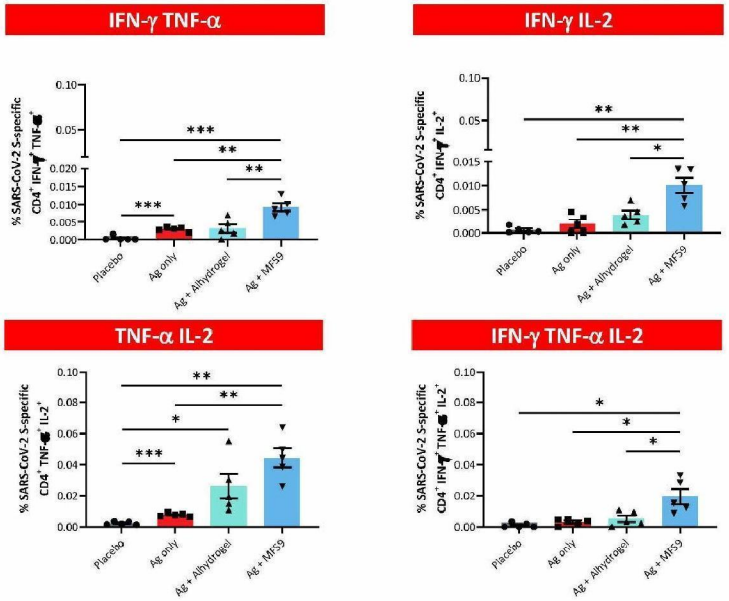
DEVELOPMENT ACTIVITIES

POLYFUNCTIONALITY OF SARS-CoV-2 S-SPECIFIC CD4+ T CELLS



Expression of multiple Th1-type cytokines

Potential correlation with lasting memory response

*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001. Each bar represents stimulated minus non-stimulated value.
Ag, antigen; IFN-γ, interferon gamma; IL-2, interleukin-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor alpha.

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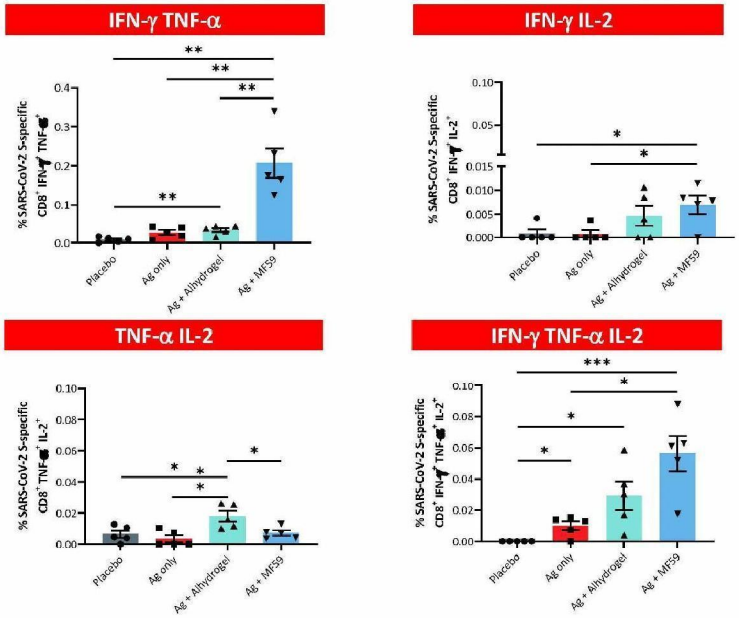
DEVELOPMENT ACTIVITIES

POLYFUNCTIONALITY OF SARS-CoV-2 S-SPECIFIC CD8+ T CELLS



Expression of multiple Th1-type cytokines

Potential correlation with lasting memory response

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Ag, antigen; IFN-γ, interferon gamma; IL-2, interleukin-2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor alpha.

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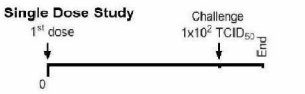
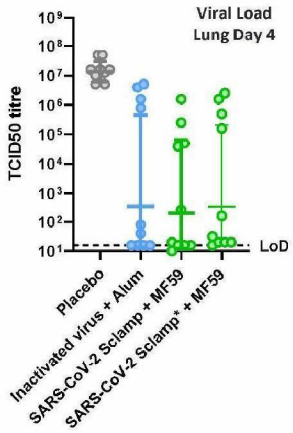
DEVELOPMENT ACTIVITIES

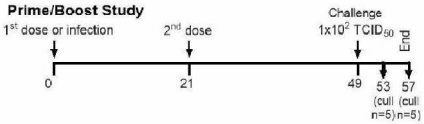
HAMSTER SARS-CoV-2 PROTECTION STUDIES
LUNG VIRAL LOAD

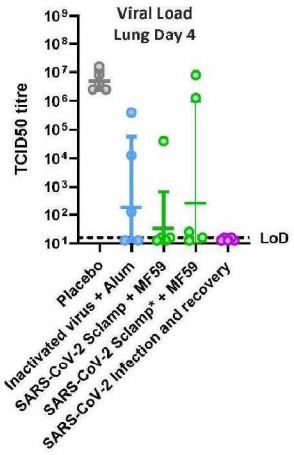
Single Dose Study

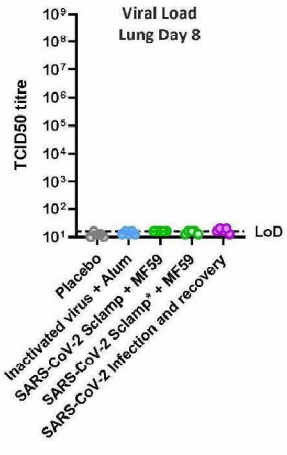




Prime/Boost Study







Low and/or below level of detection lung viral load in majority of animals after challenge with SARS-CoV-2

LoD, limit of detection; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; $TCID_{50}$, median tissue culture infectious dose.

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DEVELOPMENT ACTIVITIES

RAT GLP REPEAT DOSE TOX STUDY

FAVORABLE SAFETY PROFILE OF ADJUVANTED SARS-CoV2 SCLAMP

Study Design:

Group	Treatment	Dose Level	Allocation	Sprague Dawley Rats	Treatment Days	Termination Day
1	Saline	0	Main	10 M + 10 F	1, 15, 29	30-31
			Recovery	5 M + 5 F	1, 15, 29	43
2	SARS-CoV-2 Sclamp + MF59C.1	20 µg Sclamp + 100 µl MF59C.1	Main	10 M + 10 F	1, 15, 29	30-31
			Recovery	5 M + 5 F	1, 15, 29	43

- Three doses, 2-week interval, and 2-week recovery
- No local and systemic adverse effects
- High titer of IgG antibody responses
- Injection site observations including minimal/mild mononuclear cell and minimal myodegeneration – expected with IM adjuvanted vaccine and continuous resolution in the recovery
- The no-observed-adverse-effect level (NOAEL) is considered to be 20 µg in rats
- Second GLP repeat dose tox study is ongoing and results available in mid-Sep

Adjuvanted SARS-CoV-2 Sclamp was well tolerated in rats.

Human safety multiples of 45µg relative to rat dose is ~89-fold

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