Needs of R&D to fight COVID in Japan
Progress and challenges

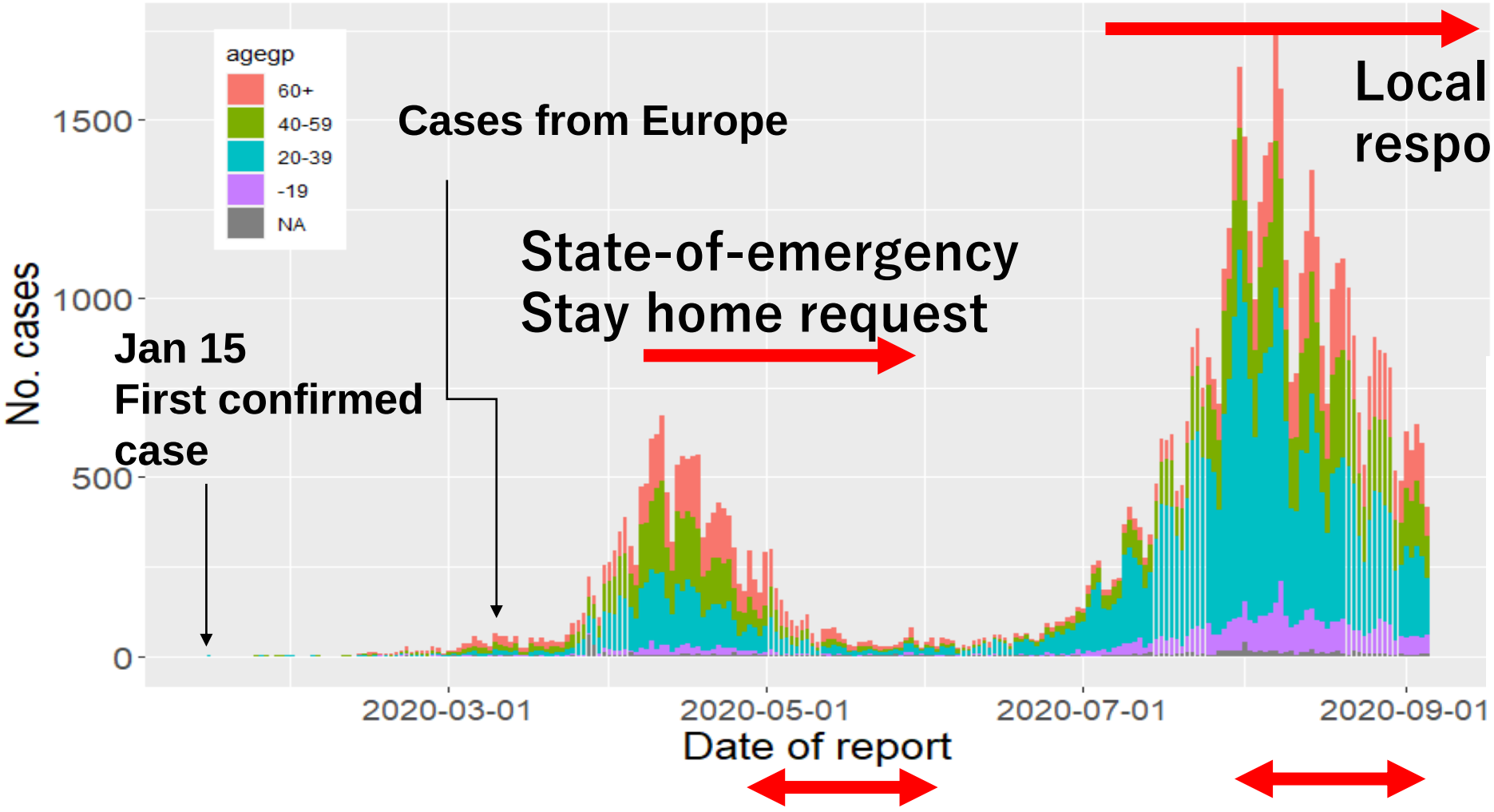
Takaji Wakita

National Institute of Infectious Diseases, Japan

Daily number of COVID-19 cases, Japan

Dr. Motoi Suzuki

Cluster surveillance



Cases from Europe

Local governors' responses

State-of-emergency
Stay home request

Jan 15
First confirmed case

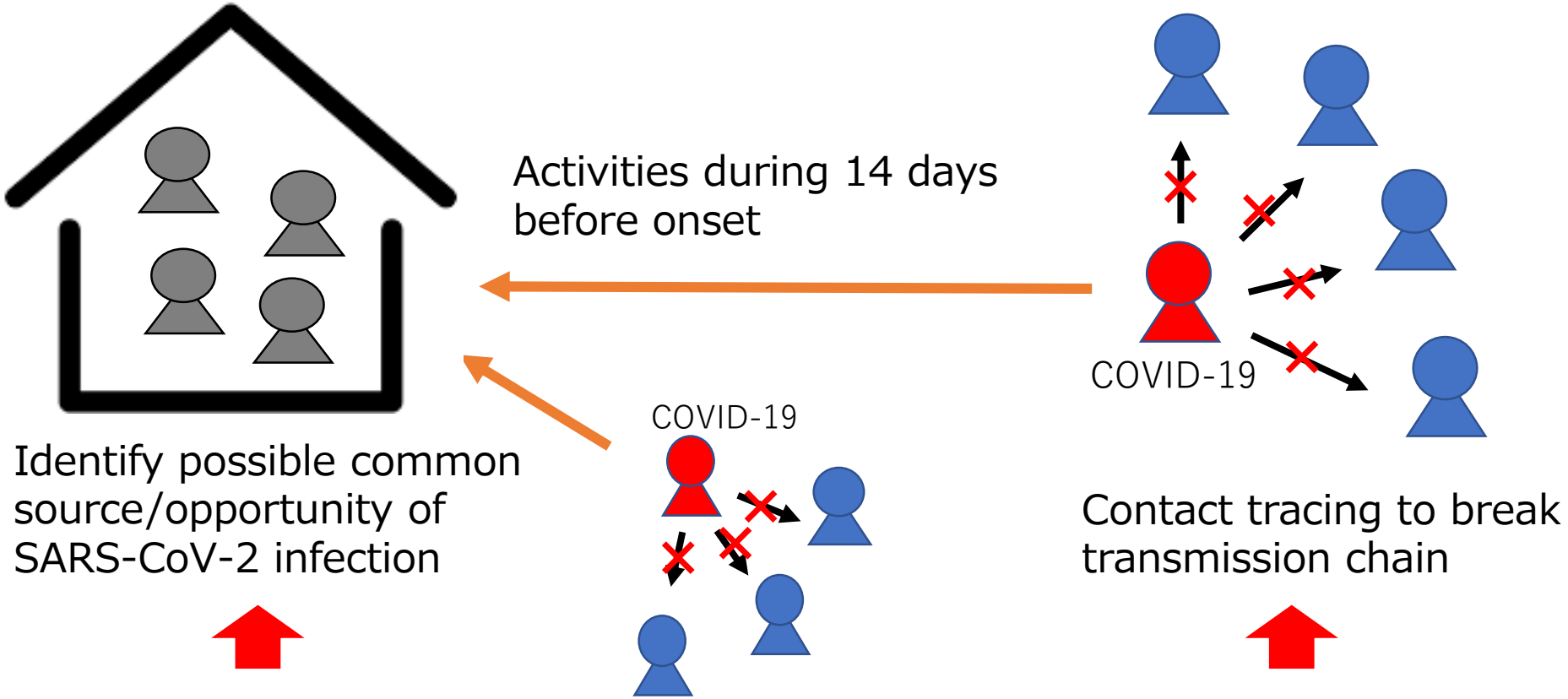
Total cases (Sep 12)
74,544 (590 / 1M)

Total deaths (Sep 12)
1,423 (11 / 1M)

Adjusted CFR: 7.2%

Adjusted CFR: 0.9%

Concept of “cluster detection and containment”



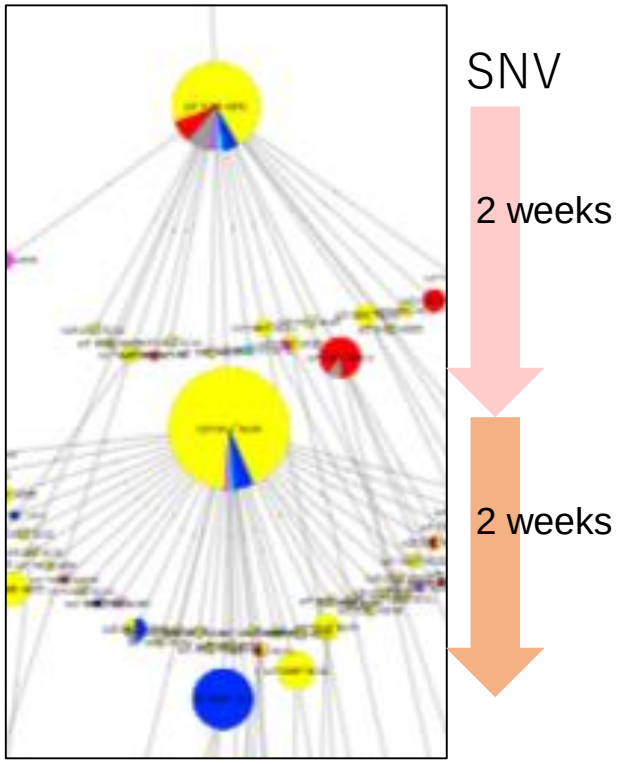
Dr. Tomoe Shimada, NIID, IDSC

Molecular Tracing of COVID-19 cases: A genome epidemiological study of SARS-CoV-2 using whole genome sequencing (WGS)

Premise

Mode of molecular evolution on the SARS-CoV-2 genome: single mutation every 2 weeks, in a random manner

SARS-CoV-2 genome



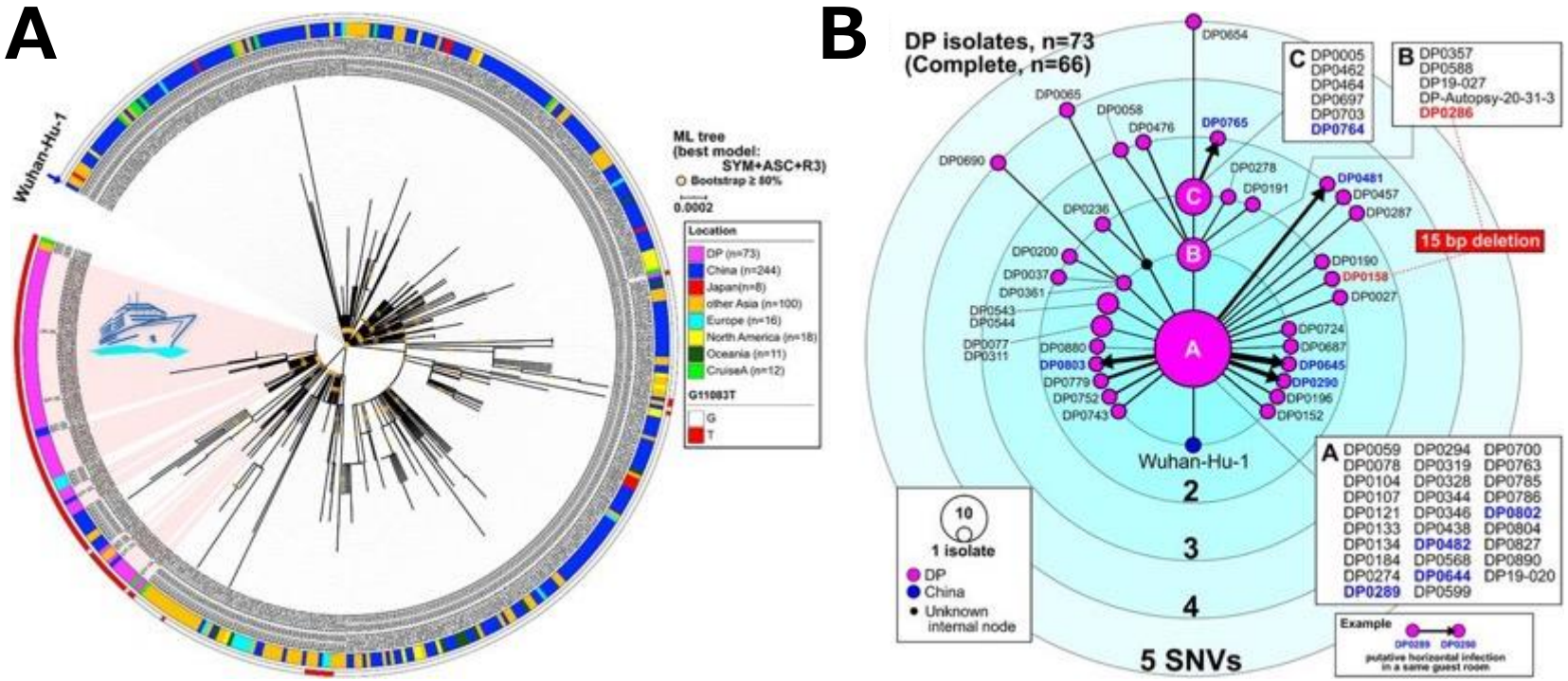
Step 1. Link cases or clusters with molecular epidemiology

- ✓ **To prove suspected epidemiological links and support epi investigations (time, place and person)**

Step 2. Inform response decision-making for targeted interventions

Dr. Makoto Kuroda, Pathogen Genomics Center, NIID

Haplotype network analysis of viral gnomes in Diamond princess Cruise ship outbreak

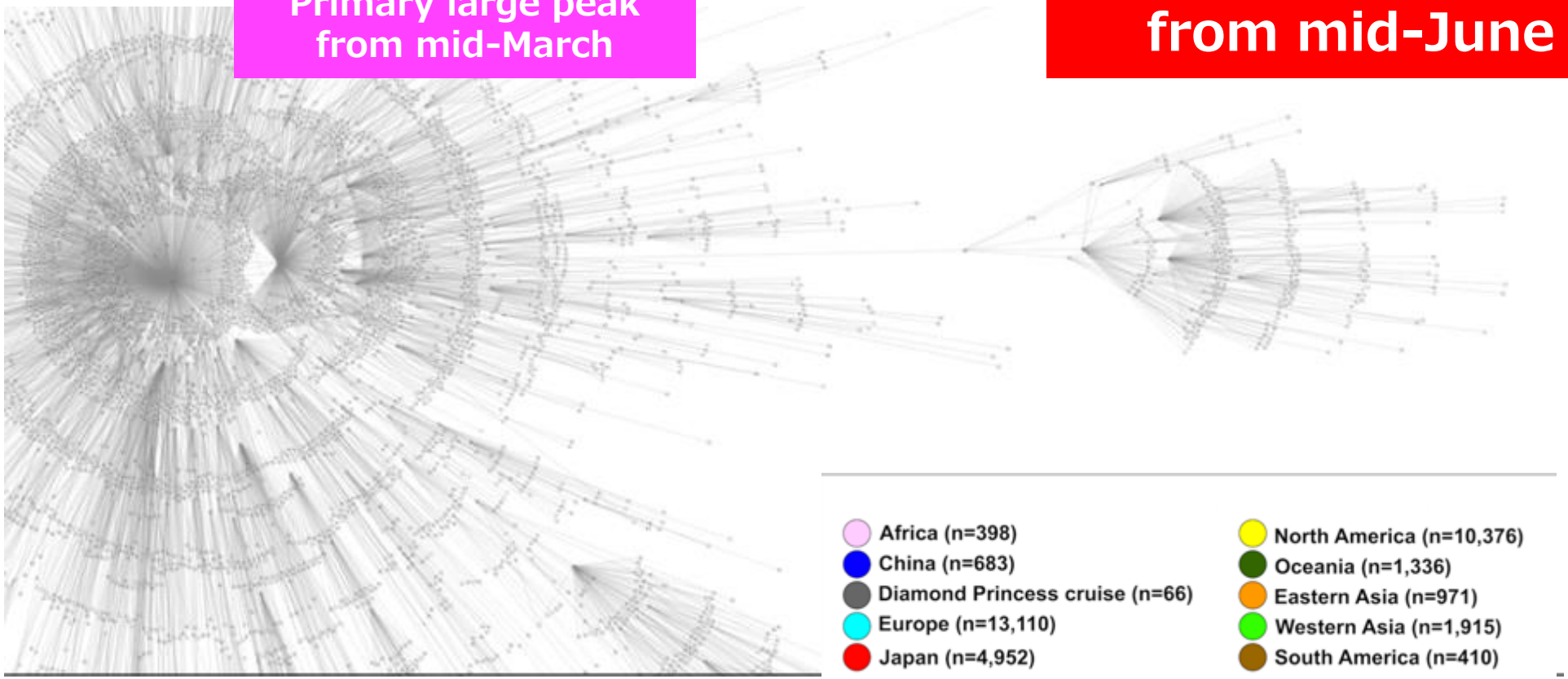


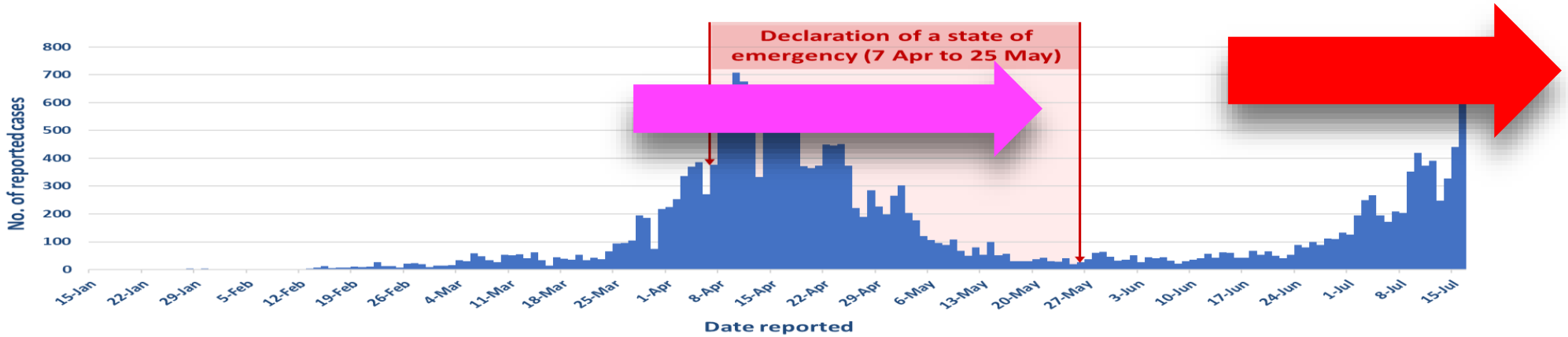
Phylogenetic analysis **SNV network analysis**

Tsuyoshi Sekizuka et al. PNAS 2020;117:33:20198-20201

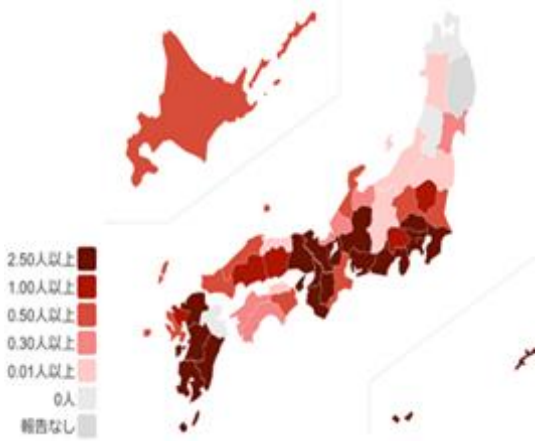
Primary large peak from mid-March

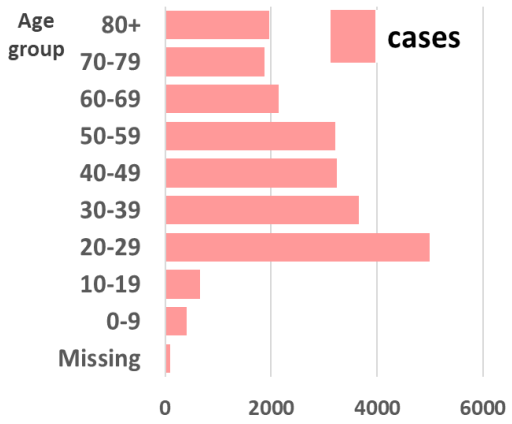
Secondary peak from mid-June





Combination of epidemiological characteristics and whole genome sequence



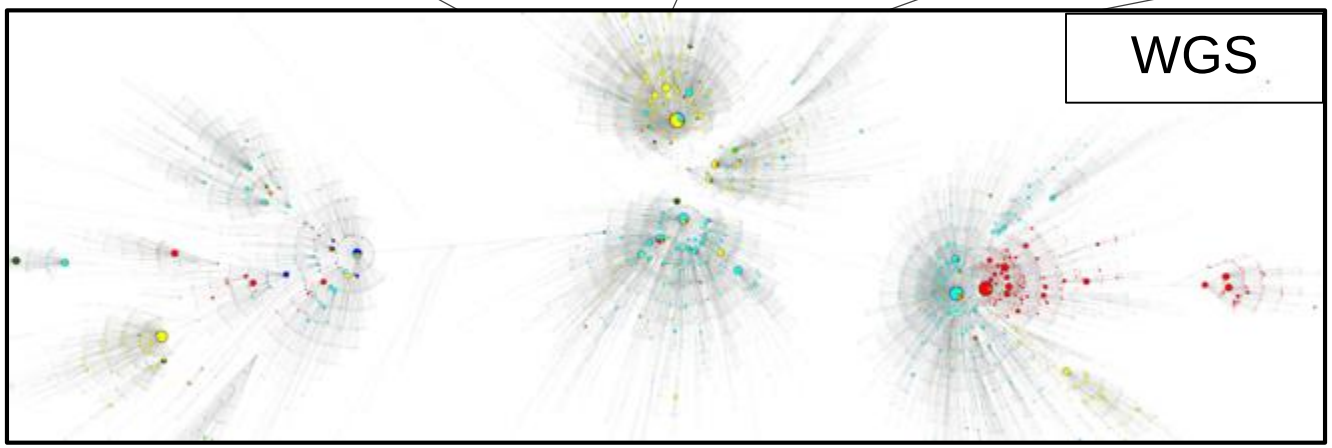


Geographic distribution

Age distribution

Clusters

Imported/ domestic



- **Multi-source surveillance**
- Detailed transmission dynamics
- Design of strategy

Identification of anti-SARS-CoV-2 drugs from drug-repositioning

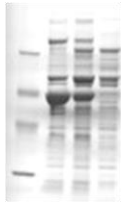
Compounds

Pharmaceutical companies (> 30)

Hokkaido University
Chiba Cancer Research Center
Tokyo University of Science
University of Tokyo
National Cancer Center
RIKEN
Nihon University
Chubu University
Kyoto University
Osaka University
Okayama University
AMED・BINDS

Virology

National Institute of Infectious Diseases

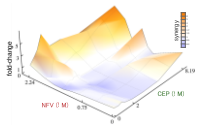


Biochemistry

RIKEN, Hokkaido U.
Kyushu U.

in silico, Informatics

RIKEN, AIST, NAIST
Nagahama U.
Tokyo U. Sci.



Mathematics

Kyushu U., NCGM
U. Tokyo, Indiana U

Clinics

Nagasaki U.

Approved Drugs
Unique compounds → Anti-COVID-19 agents → Mechanisms of virus infection/replication

Dr. Koichi Watashi
(Dept Virol II, NIID)

Higher antiviral activity of NFV and CEP than the current drug candidates

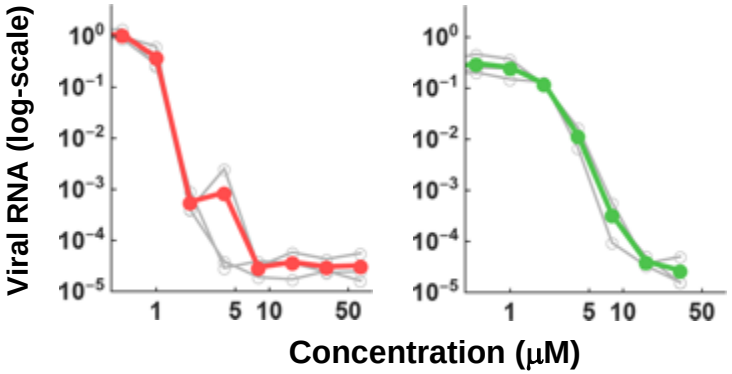
306 compounds

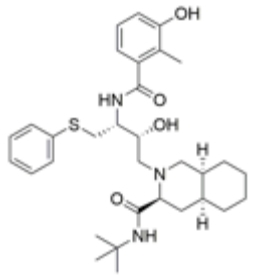
⇩

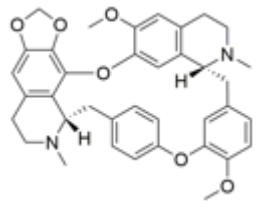
5 compounds

Nelfinavir

Cepharanthine







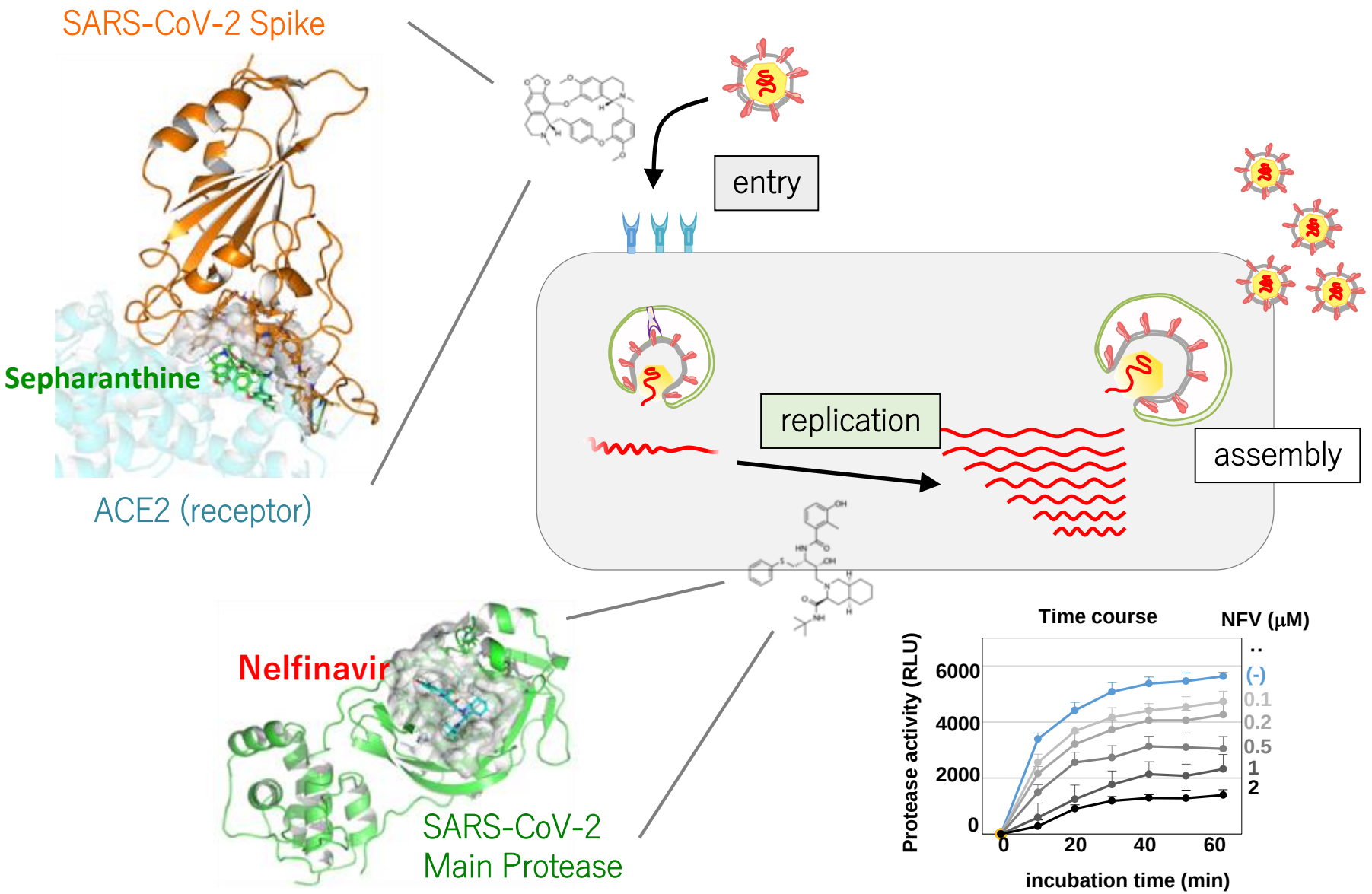
IC_{50}= 0.77 μM
IC_{90}= 1.18 μM

IC_{50}= 0.35 μM
IC_{90}= 0.91 μM

< Antiviral activity >

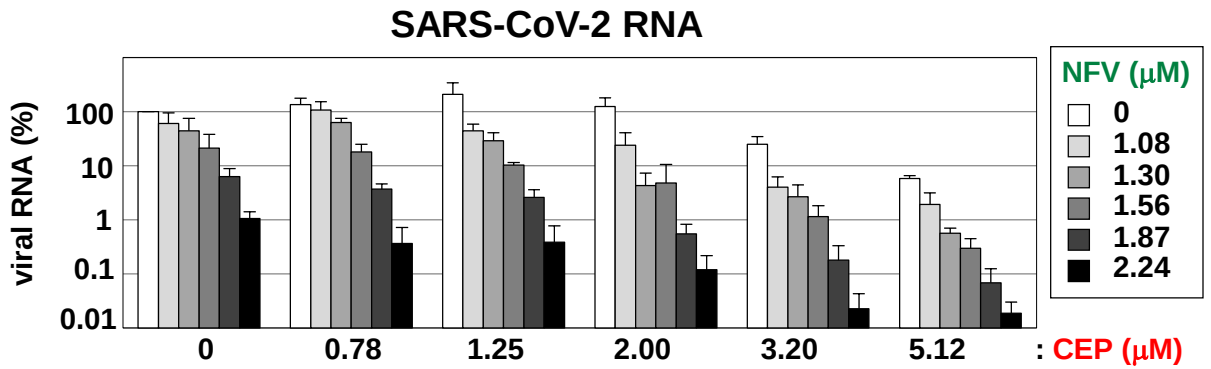
	IC_{50} (μM)	**IC_{90} (μM)**
Remdesivir	1.81	**3.89**
Favipiravir (Avigan®)	> 64	**> 64**
Ciclesonide (Alvesco®)	3.67	**6.82**
Hydroxychloroquine (Plaquenil®)	2.04	**7.05**
Lopinavir (Kaletra®)	1.73	**3.61**
Nelfinavir (Viracept®)	0.77	**1.18**
Cepahanthine (Cepahanthin®)	0.35	**0.91**

Target molecules of NFV and CEP

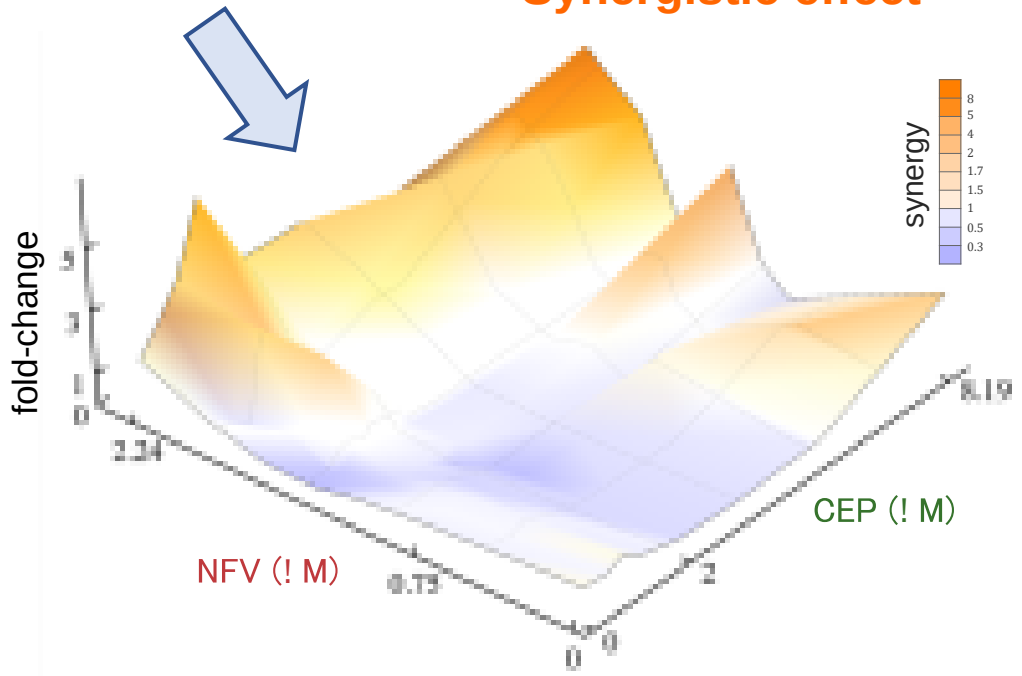


Synergistic antiviral effect of NFV/CEP combination

Improvement of antiviral therapy → Multidrug treatment

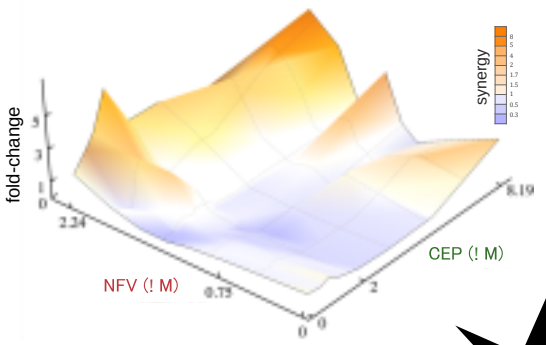


Synergistic effect

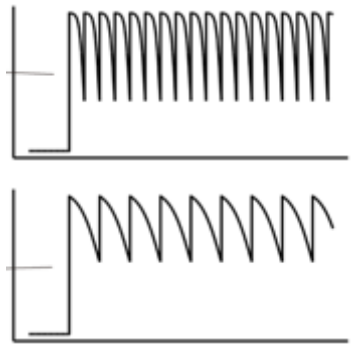


Estimated antiviral effect in clinical settings

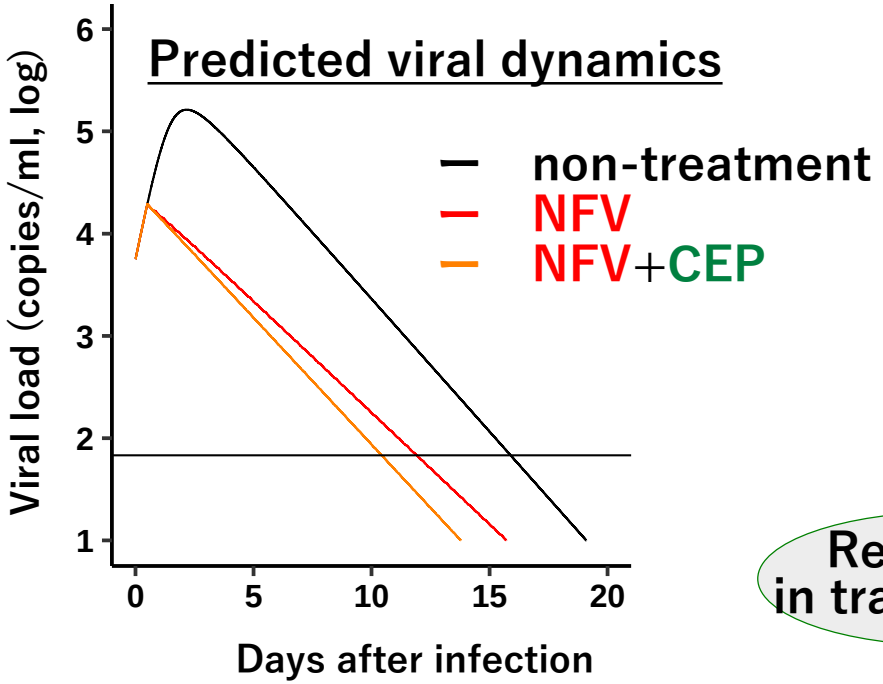
Dose-response curve



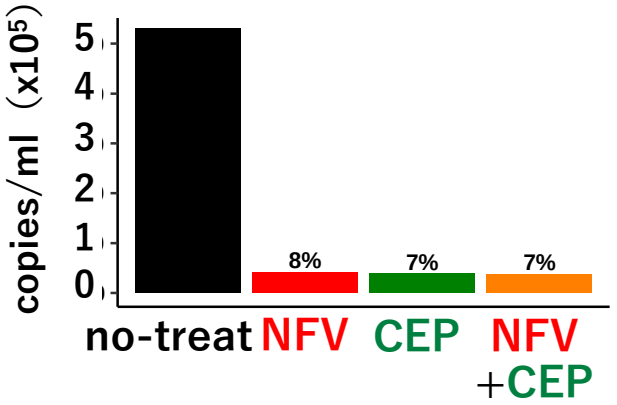
Pharmacokinetics in clinical



Predicted viral dynamics



Cumulative viral load



Reduction in transmission

Improved treatment

The paper is already on line

https://www.biorxiv.org/content/10.1101/2020.04.14.039925v1

New Results

Comment on this paper

Multidrug treatment with nelfinavir and cepharanthine against COVID-19

Hirofumi Ohashi, Koichi Watashi, Wakana Saso, Kaho Shionoya, Shoya Iwanami, Takatsugu Hirokawa, Tsuyoshi Shirai, Shigehiko Kanaya, Yusuke Ito, Kwang Su Kim, Kazane Nishioka, Shuji Ando, Keisuke Ejima, Yoshiki Koizumi, Tomohiro Tanaka, Shin Aoki, Kouji Kuramochi, Tadaki Suzuki, Katsumi Maenaka, Tetsuro Matano, Masamichi Muramatsu, Masayuki Saijo, Kazuyuki Aihara, Shingo Iwami, Makoto Takeda, Jane A. McKeating, Takaji Wakita

doi: https://doi.org/10.1101/2020.04.14.039925

Abstract | Full Text | Info/History | Metrics | Preview PDF

→ **Clinical study (jRCT2071200023)**

Evaluation of Nelfinavir for asymptomatic and mild COVID-19

A multicenter open-label, blinded outcome, randomized controlled trial (Nagasaki University)

Message

Replication inhibitor + **Entry Inhibitor** → **Synergistic antiviral effect**

Nelfinavir

oral

Cepharanthine

injection

Replaceable to an **oral drug**?

- We identified other approved drugs from ~3100 non-approved compounds

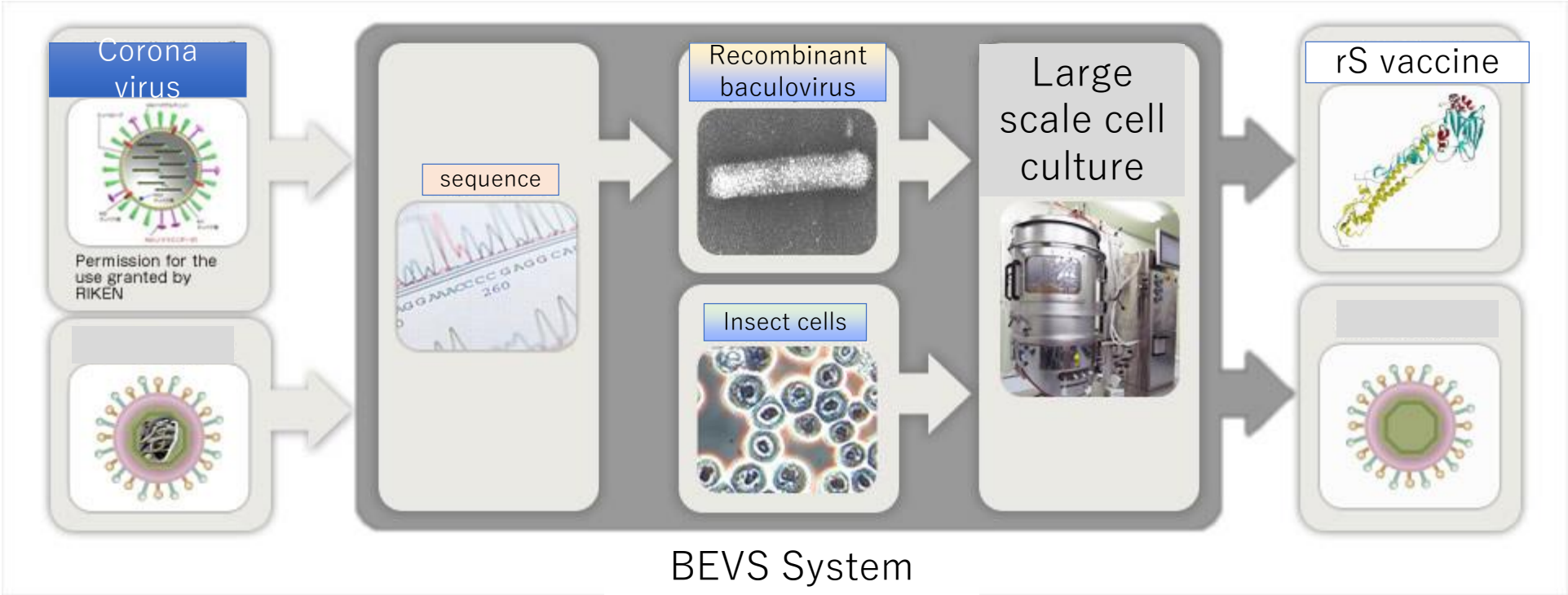
Concerns for SARS-CoV-2 Vaccine Development

- No vaccine for the similar coronaviruses such as SARS-CoV or MERS-CoV.
- SARS-CoV-2 need BSL3 facility to produce inactivated vaccine.
- Low growth rate of the virus　(2x10^7TCID50/ml) was reported.
- Disease enhancement by the vaccine is reported in SARS and MERS vaccine research.

H Hasegawa, T Suzuki, N Nagata, N Iwata, NIID

Production of SARS-CoV2 Spike protein by Baculovirus Expression Vector System

Baculovirus Expression Vector System: BEVS



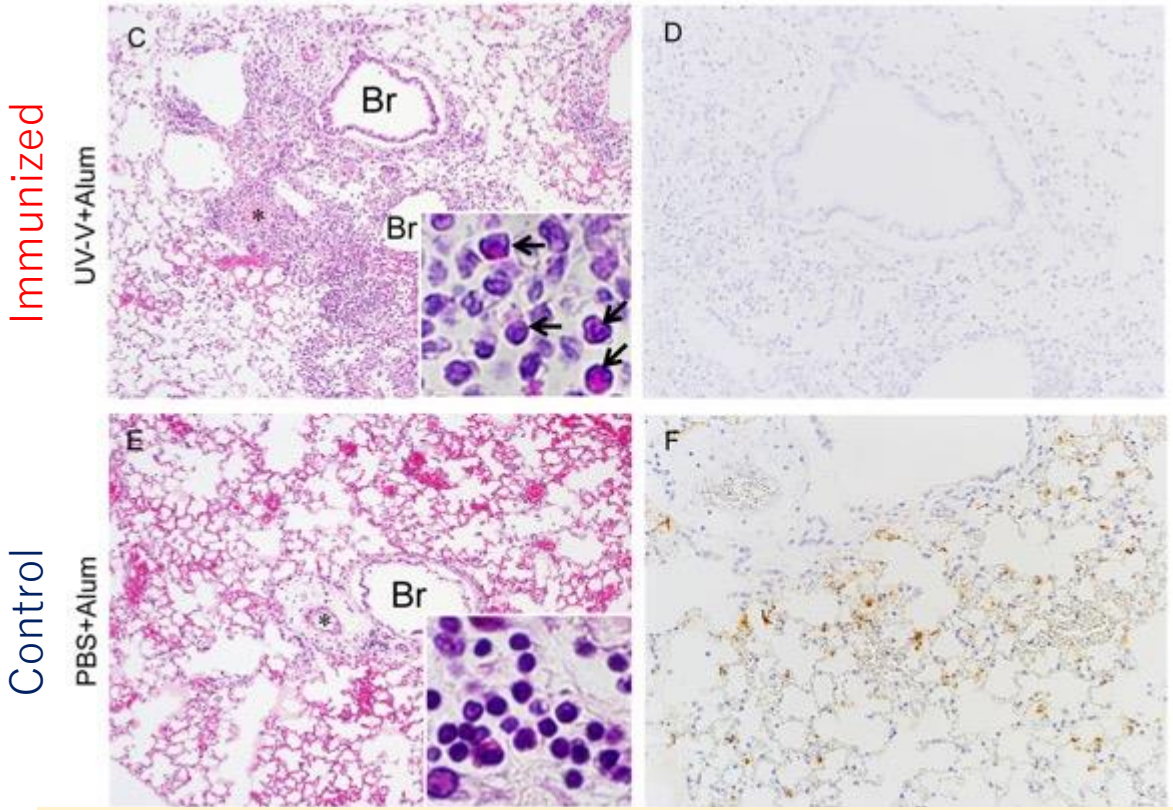
BEVS System

Examples of vaccine produced by BEVS

- ✧ Human papillomavirus vaccine
- ✧ Recombinant Influenza HA vaccine

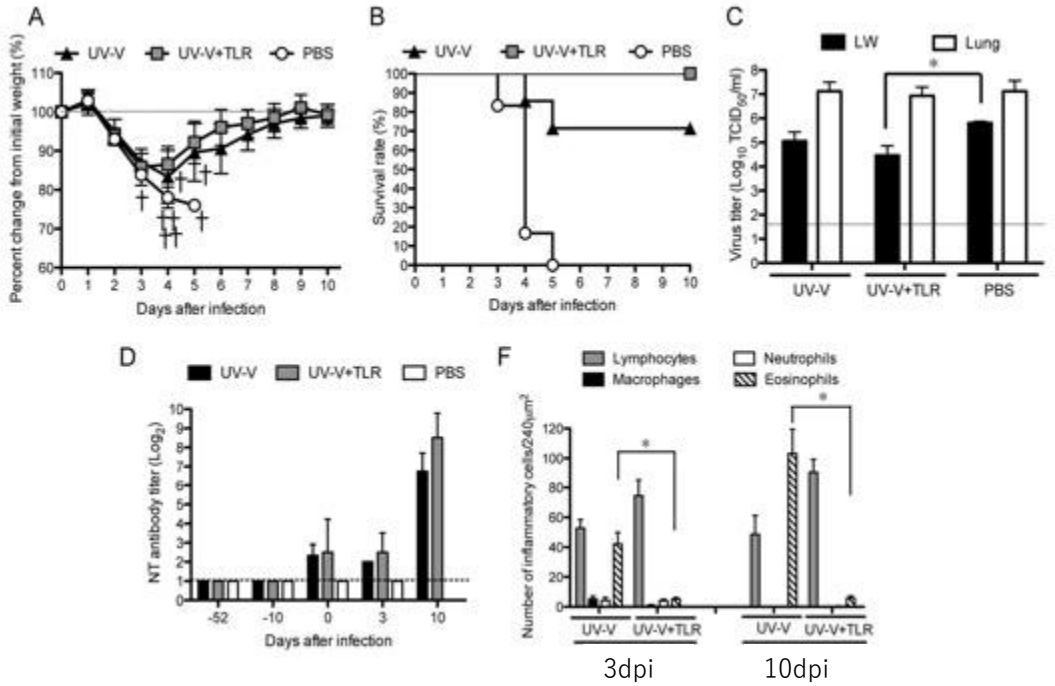
Eosinophilic infiltration after SARS-CoV infection to immunized mice

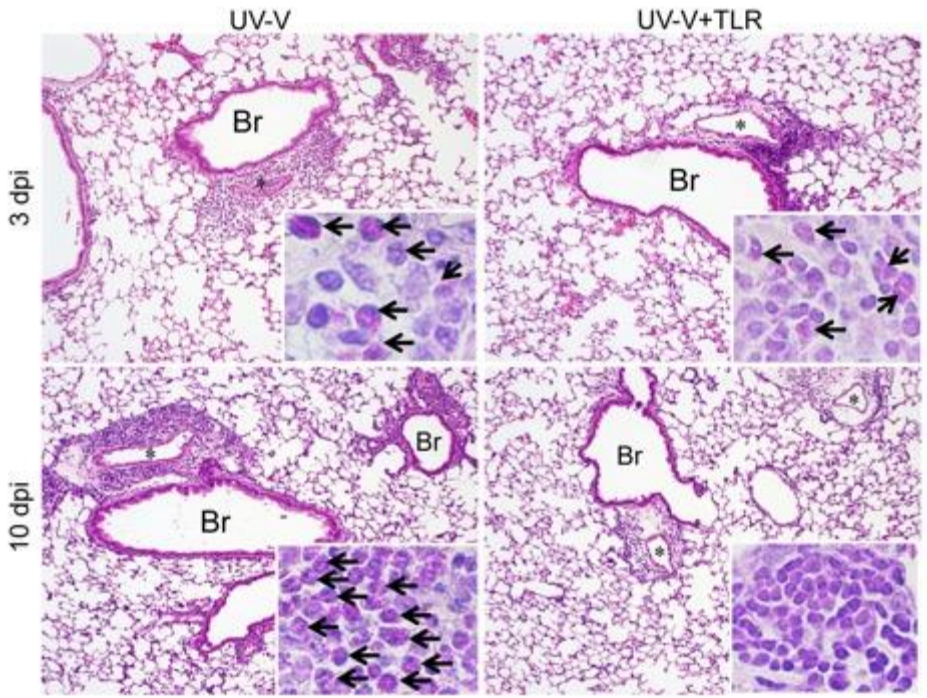
Iwata-Yoshikawa *et al.*, J Virol, 2014. 88:8597-614



Th1/Th2 balance may affect the severity of eosinophilic infiltration in immunized and infected mice, which exacerbate the pneumonia by SARS-CoV.

TLR agonist enhance the immunogenicity of vaccine and reduce vaccine derived side effects





Iwata-Yoshikawa *et al.*, J Virol, 2014. 88:8597-614
Sekimukai *et al.*, Microbiology and Immunology, 2020

Summary

- R&D is most important to fight COVID-19
- Viral genome epidemiology of SARS-CoV-2 may support cluster surveillance
- Novel anti-viral therapy is necessary using combination of compounds with different mode of actions
- Vaccine development is rapidly ongoing, however, vaccine efficacy and safety are most important