IDRIC

감염병연구기관국제심포지엄

International Symposium for Infectious Diseases Research Institutes Cooperation

1st International Symposium for Infectious Diseases Research Institutes Cooperation

감염병연구기관 국제심포지엄

February 22 - February 23, 2023

The Maison Glad Jeju

(Crystal Hall, Main bulding 2nd floor)

Korea Disease Control and Prevention Agency
National Institute of Health
National Institute of Infectious Diseases

NIH National Institute of Allergy and Infectious Diseases

STATENS SERUM INSTITUT

National Centre for Infectious Diseases

축 사

Good morning, distinguished colleagues, ladies and gentlemen, I am Youngmee Jee, Commissioner of Korea Disease Control and Prevention Agency (KDCA).

First of all, I would like to congratulate the Korea National Institute of Infectious Diseases for organizing the 1st International symposiumin Jeju Island. I want to thank distinguished speakers from NIAID United States for traveling a long way to attend this symposium and also want to welcome infectious disease experts from NCID Singapore, SSI Denmark for joining this symposium online and our experts from Korea for joining this symposium in person. I have to make an apology that I am not able to join this important symposium and meet speakers and chairpersons in person.

This international symposium organized by Korea NIID is a truly meaningful event after three years of many online virtual meetings and symposiums during COVID19 pandemic.

I want to thank the staff members of "the National Institute of Infectious Diseases" for working extremely hard to prepare this two day symposium and the expert workshop.

오늘 개최되는 제1회 감염병연구기관 국제심포지엄은 국립감염병연구소가 설립되고 처음으로 개최하는 국제행사로, 코로나19로 인해 전 세계의 국가 연구소 간 긴밀한 소통과 협력이 중요해지고 있는 상황에서 다양한 공동네트워크를 구축하고, 실질적인 협력방안을 모색하기 위한 중요한 행사입니다.

작년말 글로벌보건안보구상(GHSA) 장관급 회의에서도 30여개 참여 국가들은 감염병 대응을 위해 보건안보 차원에서의 접근이 필요하고, 미래팬데믹 대비·대응를 위해 국제적인 연대와 협력 강화가 필수적이라는 데 모두 의견을 모았습니다.

코로나19가 이제 안정화되어 일상회복단계로 가고 있습니다만 기후와 환경변화 등 다양한 요인으로 인해 발생할 수 있는 신종감염병은 계속 인류를 위협하고 있습니다. 코로나19 판데믹에서 경험한 것처럼 신종감염병의 극복을 위해서는 방역과 의료 대응 역량 이외에도 안전하고 효과적인 백신과 치료제의 신속한 개발과 사용은 필수적입니다.

한국을 포함한 많은 국가들이 포스트 코로나를 준비하는 가운데 국립감염병연구소가 미국 NIAID, 싱가포르 NCID, 덴마크 국립혈청연구소와 백신·치료제 개발 등에 대한 최신 연구결과를 공유 할 수 있는 장을 마련한 것은 매우 시의적절하다고 생각합니다.

질병관리청이 국정과제인 감염병 대응체계 고도화라는 중차대한 역할을 추진하고 있는 가운데 새롭게 출범한 국립감염병연구소도 국내외 감염병 연구기관 간 긴밀한 협력체계 구축을 통해 국제공조를 주도하고 감염병 연구의 국가콘트롤타워 역할을 할 수 있기를 기대합니다.

축 사

아무쪼록 이번 심포지엄을 통해 국내외 감염병 연구기관 간 실질적인 연구협력 기회가 확대되고 감염병에 신속하고 효율적으로 대응할 수 있는 국제연구협력네트워크가 마련되길 기대합니다.

심포지엄에 참석하신 모든 분들의 건강과 행복을 기원합니다. 감사합니다.

I wish you all the best. Thank you.

Commission of KDCA, **지영미**

질병관리청장 **지 영 미**

개 회 사

안녕하십니까.
국립감염병연구소장 장희창입니다.

먼저 먼저 바쁘신 일정에도 불구하고 제1회 감염병연구기관국제심포지엄(IDRIC)에 참석하여 주신 내·외빈 여러분께 진심으로 감사의 말씀을 드립니다. 오늘 개최되는 국제심포지움은 국립감염병 연구소가 설립되고 처음으로 주최하는 국제행사로 미국 국립알레르기감염병연구소, 싱가포르 국립감염병센터 그리고 덴마크 국립혈청연구소와 함께 다양한 연구성과를 공유하고 향후 기관간 실질적인 협력을 위한 방안논의를 목표로 하고 있습니다.

최근 코로나 19 등 감염병의 유행은 한 국가에만 한정된 문제가 아니라 전 세계가 공동대응해야 하는 부분이라는 점에 참석하신 많은 분들이 동의하실 거라고 생각합니다. 특히, 감염병 연구개발은 국가마다 신속한 병원체 확보와 연구현황 파악이 중요한만큼 국제연대 강화가 필요합니다.

특히, 미국과는 지난 해 4월 협력의향서(LOI)를 체결한 이후 보다 활발하게 공동연구를 협의해왔으며, 연구소 간 관계를 돈독히 하기 위해 이러한 자리를 마련하게 되었습니다. 연구소에서는 미국의 첨단기술과 한국의 우수한 자원 및 인프라를 효과적으로 연계하기 위하여 지속적인 공동연구, 인적교류, 지식 및 정보교환 활동을 지원하고자 합니다.

향후 미국을 포함하여 싱가포르, 덴마크와 협력하여 신종감염병의 치료제와 백신개발에 앞장서고, 미해결 감염병에 대한 더욱 실질적인 연구 협력을 추진 할 수 있는 기반을 마련하는 계기가 되길 바랍니다.

끝으로, 다음 심포지엄에서는 금번에 참석하지 못한 전문가 분들도 함께 모시고 감염병 연구개발을 논의할 수 있는 날이 오기를 희망합니다. 이 자리를 준비해주신 분들의 노고에도 깊은 감사를 드리며, 모든 분들의 건강과 행복을 기원합니다. 감사합니다.

국립감염병연구소장 **장 희 창**

National Institute of Infectious Diseases(NIID)

Key Strategies and Projects

R&D planning management

- One-stop management of national infectious disease R&D strategies, investment, and performance
- Bolster authority to support collaborating agencies in the Industry, academia, research, and hospitals

Improve objective-based research investment system

- Facilitate R&D for emerging and variant infectious diseases
- Unify policy objectives for unresolved infectious diseases and promote achievement

A control tower for infectious disease research to ensure national health security

Enhance researcher expertise

- Cultivate and secure professional manpower
- Shape a researcher-centered organization
- Professionalize R&D administrative support

Bolster basis for collaboration

- Improve research environment, address Congress hearings, audits, strategic planning
- Host events and seminars
- Promote interaction and collaboration among industry, academia, and research

Infrastructure

Center for Vaccine Research

National Culture Collection for Pathogens

International Symposium for Infectious Diseases Research Institutes Cooperation

As the control tower for national infectious disease research to secure "vaccine sovereignty," we develop measures and produce scientific evidence for the prevention of and prompt response to infectious diseases. We investigate not only emerging and variant infectious diseases but also unresolved infectious diseases, vectors, and drug resistance, and conduct diverse clinical trials.

Research objectives

- Predict, prepare for, and ensure quicker response to novel and variant infectious diseases
- Secure key technologies to conquer unresolved infectious diseases
- Raise the national reputation by leading international research collaboration
- Secure a rich pool of pathogens and clinical resources and advance collaborative activities

Basic application

- Basic, application, and translational research for the prevention and treatment of infectious diseases
- Secure technologies to respond to emerging and variant infectious diseases
- Strengthen R&D competence to manage unresolved infectious diseases
- Step up research for developing a safety net for national infectious diseases
- Promote international collaboration to facilitate infectious disease research

National Institute of Allergy and Infectious Diseases (NIAID)

The National Institute of Allergy and Infectious Diseases (NIAID) is one of the 27 Institutes and Centers of the U.S. National Institutes of Health (NIH), U.S. Department of Health and Human Services. It was originally established in 1948 as The National Microbiological Institute, which became NIAID in 1955. NIAID conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. This research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world. NIAID is composed of seven research divisions: The Division of AIDS (DAIDS); the Division of Allergy, Immunology, and Transplantation (DAIT); the Division of Clinical Research (DCR); the Division of Extramural Activities (DEA); the Division of Intramural Research (DIR); the Division of Microbiology and Infectious Diseases (DMID); and the Dale and Betty Bumpers Vaccine Research Center (VRC). DAIDS, DAIT, and DMID direct and manage grants, contracts, and cooperative agreements that support research at external academic and research institutions (known as extramural research), while DCR, DIR, and the VRC conduct studies and clinical investigations within NIAID laboratories (known as intramural research).

Following Dr. Anthony Fauci's retirement as the Director of NIAID on December 31, 2022, Dr. Hugh Auchincloss has assumed the role of Acting Director of NIAID. He has served as NIAID's Principal Deputy Director since joining NIH in 2006 and has played a key role in research planning and implementation activities, including helping to prepare and support a strategic vision for NIAID, and contributing to the management of NIAID's extensive portfolio of basic, clinical, and applied research and product development activities.

Statens Serum Institute (SSI)

Statens Serum Institut (SSI) is a public health preparedness and research institute under the auspices of the Danish Ministry of Interior and Health. The Institute's main duty is to ensure preparedness against infectious diseases and biological threats as well as control of congenital disorders. Its mission is to strengthen health through disease control and research. As such, all of SSI's activities are grounded in research and each year, the institute publishes around 400 scientific articles. Established in 1902 to secure the production and supply of anti-diphtheria serum to Danish patients, SSI has been incremental in fighting infectious diseases in Denmark for 120 years.

National Centre for Infectious Diseases (NCID)

Photo credit: National Centre for Infectious Diseases

The National Centre for Infectious Diseases (NCID) is a purpose-built facility designed to strengthen Singapore's capabilities in infectious disease management and prevention. NCID houses clinical services, public health, research, training and education and community engagement functions under one overarching structure. In addition to the clinical treatment of infectious diseases and outbreak management, the expanded roles and functional units of NCID include the National Public Health and Epidemiology Unit, the National Public Health Laboratory, the Infectious Disease Research and Training Office, the Antimicrobial Resistance Coordinating Office, and the National Public Health programmes for HIV and Tuberculosis. Benchmarked to international standards and best practices, NCID will enhance Singapore's ability to effectively manage infectious diseases.

Visit www.ncid.sg for more information.

□ Day 1(22, Feb)

Time(KST)	Program		
09:00-09:30	Registration		
09:30-10:10	Opening Remarks		
10:10-10:30	Presentation Session 1(Virtual) : Building a novel pandemic preparedness program	Speaker : Dr. Daniel Douek (NIAID, USA)	Chair: Woo-joo Kim, M.D., PhD.
10:30-10:40	Q&A		
10:40-11:00	Presentation Session 2 : Development of therapeutic human monoclonal antibodies against SFTSV infection	Speaker : Dr. Han-saem Lee (NIID, Korea)	
11:00-11:10	Q&A		
11:10-11:30	Presentation Session 3 : Bacteriophages and Endolysins Combating Multidrug Resistant (MDR) Pathogens	Speaker : Dr. Hee-joon Myung (LyseNTech, Korea)	Chair: Myoung-don Oh, M.D., PhD.
11:30-11:40	Q&A		
11:40-12:00	Presentation Session 4 : NIH-Supported Clinical Trial of Phage Therapy for Cystic Fibrosis Begins	Speaker : Dr. Dennis M. Dixon (NIAID, USA)	
12:00-12:10	Q&A		
12:10-13:30	Lunch		
13:30-13:50	Presentation Session 5 : Flagellin as a potent immune modulator for the elderly	Speaker : Dr. Kyung-a Cho (Medispan Inc., Korea)	Chair: Baik-lin Seong, M.D., PhD.
13:50-14:00	Q&A		
14:00-14:20	Presentation Session 6 : Vaccine adjuvants research	Speaker : Dr. Kentner Leroy Singleton (NIAID, USA)	
14:20-14:30	Q&A		
14:30-14:50	Presentation Session 7 : The future of pandemic preparedness: Building collaborations and EV-D68 as a test case for NIAID/VRC's PREMISE program	Speaker : Dr. Alicen Spaulding (NIAID, USA)	
14:50-15:00	Q&A		
15:00-15:10	Break		
15:10-15:40	Panel Discussion		
15:40-17:10	Meeting to Discuss Potential Collaborations		
17:10-18:10	Break		
18:10-	Dinner		

□ Day 2(23, Feb)

Time(KST)	Program		
09:00-09:45	Registration		
09:45-09:55	Opening Remarks		
09:55-10:10	Presentation Session 1 : One Health approach to antimicrobial resistance	Speaker : Dr. Eun-Jeong Yoon (NIID, Korea)	Chair: Shin-woo Kim, M.D., PhD.
10:10-10:20	Q&A		
10:20-10:35	Presentation Session 2(Virtual) : One Health Antimicrobial Resistance research landscape in Singapore	Speaker : Dr. Selina Poon (NCID, Singapore)	
10:35-10:45	Q&A		
10:45-11:00	Presentation Session 3(Virtual) : Population CPE evolution in Singapore	Speaker : Dr. Ng Oon Tek (NCID, Singapore)	
11:00-11:10	Q&A		
11:10-11:20	Break		
11:20-11:35	Presentation Session 4 : Long COVID Research Projects in NIID	Speaker : Dr. So-Young Lee (NIID, Korea)	Chair: Jun-yong Choi, M.D., PhD.
11:35-11:45	Q&A		
11:45-12:00	Presentation Session 5(Virtual) : Long COVID treatment trials: pathogenesis guides intervention	Speaker : Dr. David Lye (NCID, Singapore)	
12:00-12:10	Q&A		
12:10-12:20	Break		
12:20-12:50	Discussion on future collaboration(NCID-NIID)		
12:50-13:40	Meeting to Discuss Potential Collaborations(NCID)		
13:40-15:00	Lunch		

Program

Time(KST)	Program		
15:00-15:20	Opening Remarks		
15:20-15:35	Presentation Session 1 : Serosurveillance and Immunogenicity Studies on COVID-19 in Korea	Speaker : Dr. Byoung-guk Kim (NIID, Korea)	Chair: Yeon-sook Kim, M.D., PhD.
15:35-15:50	Q&A		
15:50-16:05	Presentation Session 2(Virtual) : How to use and integrate whole genome sequencing into outbreak investigation programs - the example of CPO and VRE in Denmark	Speaker : Dr. Ute Wolff Sönksen (SSI, Denmark)	
16:05-16:20	Q&A		
16:20-16:35	Presentation Session 3 : Development of the novel Tuberculosis vaccine applied to various platforms in Korea	Speaker : Dr. Hye-Sook Jeong (NIID, Korea)	Chair: Jae-joon Yim, M.D., PhD.
16:35-16:50	Q&A		
16:50-17:05	Presentation Session 4(Virtual) : Overview of TB vaccine development	Speaker : Dr. Rasmus Mortensen (SSI, Denmark)	
17:05-17:20	Q&A		
18:00-19:00	Meeting to Discuss Potential Collaborations(SSI)		
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International Symposium for Infectious Diseases Research Institutes Cooperation

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Part 1. Emerging virus

Chair:
Woo-joo Kim, M.D., PhD.

1. Building a novel pandemic preparedness program
Dr. Daniel Douek(NIAID, USA)

2. Development of therapeutic human monoclonal antibodies against SFTSV infection
Dr. Han-saem Lee(NIID, Korea)

Part 1. Emerging virus

Moderator

Woo-Joo Kim

Professor

Division of Infectious Diseases, Department of Internal Medicine, Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea

- **EDUCATION:**

1992	Korea University Graduate School, Ph.D.
1986	Korea University Graduate School, MS
1983	Korea University College of Medicine, MD
1996 ~ 1997	Visiting Scholar, Division of Infectious Diseases, Rush-Presbyterian St. Luke's Medical Center, Chicago, IL, U.S.

- **PROFESSIONAL EXPERIENCE:**

2022 ~ Present	President, The Korean Association of Internal Medicine
2021 ~ Present	President, The Korean Vaccine Society
2021 ~ Present	Member, National Academy of Medicine of Korea
2019 ~ Present	Member, Committee for Planning Infectious Diseases Research, Korea Diseases Control Agency
2015 ~ 2017	President, Korean Society for Zoonoses
2010 ~ 2016	Director, Trans-governmental Enterprise for Pandemic Influenza, Korea
2015	Director, Rapid Response Team for MERS Control; Advisor for Prime Minister
2013 ~ 2015	Chairman, The Korean Society for Infectious Diseases
2009 ~ 2011	Vice-President, Korean Society of Nosocomial Infection Control
1999 ~ 2001	Chief, Respiratory Virus Laboratory, Korea National Institute of Health

Part 1
Emerging virus

1. Building a novel pandemic preparedness program

Dr. Daniel Douek (NIAID, USA)

Daniel César Douek

Senior Investigator and Chief(Human Immunology Section, Vaccine Research Center, NIAID, NIH) / Genome Analysis Core(Chief) / PREMISE pandemic preparedness program(Director) / Sheba Pandemic Preparedness Research Institute(Senior Scientific Advisor)

- **EDUCATION:**

1987	University of Oxford, B.A.(Physiological Sciences (Medicine))
1990	University of London, M.B.B.S.(Medicine)
1993	Royal College of Physicians, M.R.C.P.(Medicine)
1996	University of Oxford, M.A.(Physiological Sciences (Medicine))
1997	University of London, Ph.D.(Immunology)

- **PROFESSIONAL EXPERIENCE:**

1990 ~ 1993	Intern and Resident in UK
1993 ~ 1996	Honorary Registrar (Clinical Research Fellow) in Infectious Diseases, Hammersmith Hospital, London, UK
1993 ~ 1996	Wellcome Trust Clinical Graduate Training Fellowship, Dr. Daniel Altmann's laboratory, MRC Clinical Sciences Centre, Hammersmith Hospital, London, UK. Ph.D. Thesis: "MHC expression and selection events in the thymus"
1997	Postdoctoral Research Fellow, Richard A. Koup's laboratory, Aaron Diamond AIDS Research Center, The Rockefeller University, New York, USA
1997 ~ 1999	Postdoctoral Research Fellow, Richard A. Koup's laboratory, Division of Infectious Diseases, The University of Texas Southwestern Medical Center at Dallas, USA
1999	Instructor in Internal Medicine, Division of Infectious Diseases, The University of Texas Southwestern Medical Center at Dallas, USA

• PROFESSIONAL EXPERIENCE:

2000 ~ 2001	Assistant Professor in Internal Medicine, Division of Infectious Diseases, The University of Texas Southwestern Medical Center at Dallas, USA
2000 ~ 2006	Investigator and Chief, Human Immunology Section, Vaccine Research Center, NIAID, National Institutes of Health, Bethesda, USA
2007 ~ Present	Adjunct Associate Professor, Dept. of Pathology, University of Pennsylvania, Philadelphia, USA
2019 ~ 2020	Rosi and Max Varon Visiting Professor, Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel

• SUMMARY

Topic: Building a novel pandemic preparedness program Brief description of the presentation:

Abstract

I will discuss principles underlying an immunologic approach to pandemic preparedness, progress made in designing serologic assays and widening our international partnerships, an EV-D68 pilot study, and specific projects to identify neutralizing antibodies against viruses including SFTSV and Langya virus.

The Next Steps for Pandemic Preparedness

- Given the 10+ years of VRC experience and relative readiness for CoVID-19 how can we best prepare for the next emerging virus epidemic or pandemic?
- Many strategies are established, will be launched or are being discussed both domestically and globally
- PREMISE is an anticipatory reagent and countermeasure program based at the VRC

PREMISE
PANDEMIC RESPONSE REPOSITORY
MICROBIAL/IMMUNE SURVEILLANCE AND EPIDEMIOLOGY

NIH National Institute of Allergy and Infectious Diseases
Vaccine Research Center
Vaccines for Life™

PREMISE
PANDEMIC RESPONSE REPOSITORY
MICROBIAL/IMMUNE SURVEILLANCE AND EPIDEMIOLOGY

NIH National Institute of Allergy and Infectious Diseases
Vaccine Research Center
Vaccines for Life™

Goal:

- Establish a pre-emptive stockpile of tangible immunobiological countermeasures
  - Proactive to accelerate the response to potential pandemic threats

Process:

- Immune analysis of targeted human cohorts to detect reactivity against potentially pandemic viruses
- Identify immunogenic regions of and monoclonal antibodies specific for potentially pandemic viruses

Publicly accessible deliverables:

- Immunogens suitable for vaccine discovery and development
- Monoclonal antibodies with potential for prevention and therapy
- Reagent and data resources for early detection and diagnostic assays

What PREMISE is Not

- A global sero-surveillance network
- An early warning system to detect imminent pandemic threats
- A prototype pathogen approach to vaccine design
- However, PREMISE closely interacts with all these approaches to achieve the three deliverables

Strategies, Objectives and Deliverables of PREMISE

Resources and tools:

1. **Serum and immune cells**: general population cohorts and targeted cohorts at risk of exposure to emerging pathogens
2. Development of **high throughput multiplexed serological and cellular immune assays**
3. Genetic analysis of **zoonotic reservoirs** and **symptomatic humans** for pathogen discovery

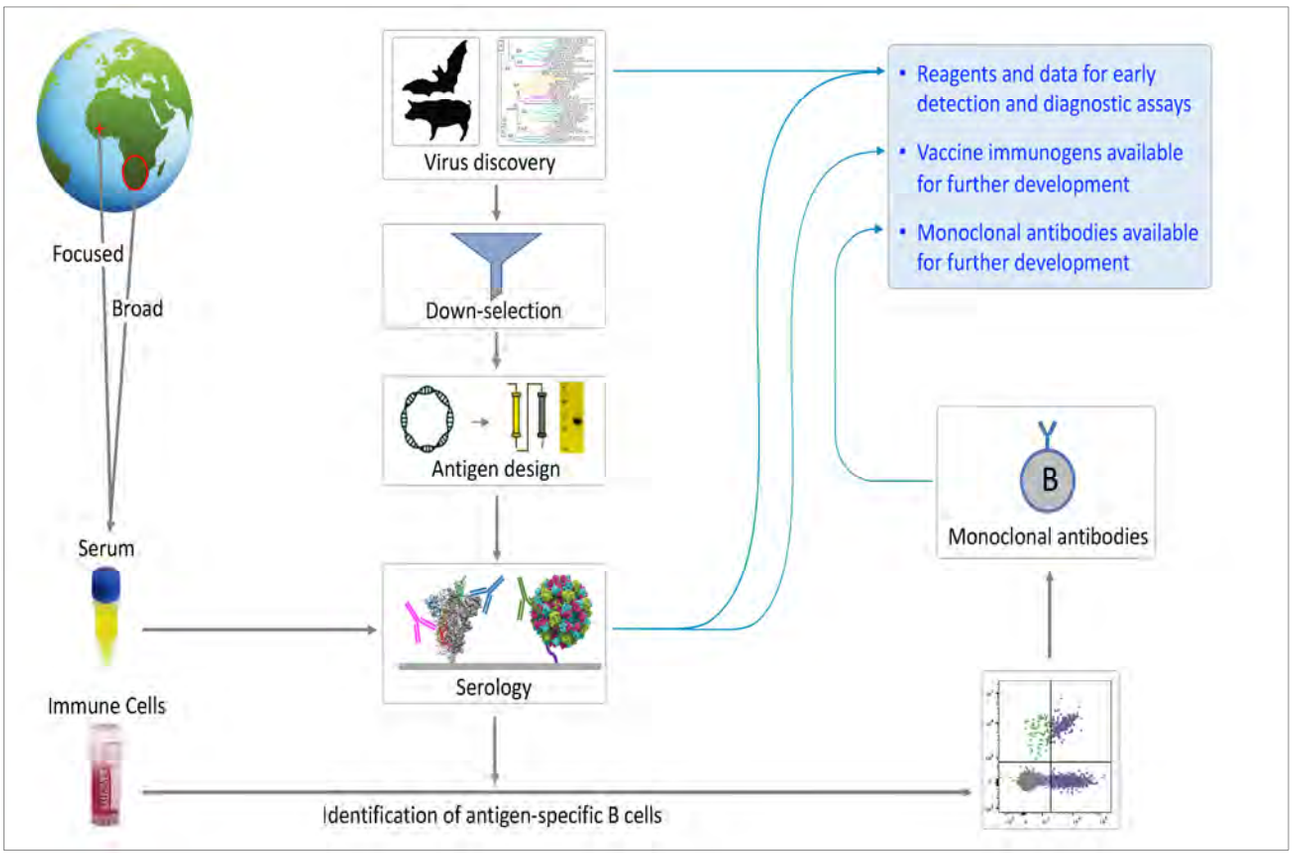
Serologic and cellular immune discovery against a broad array of pathogens and selected variant strains:

1. **Antigen-specific responses** to pathogens that occasionally enter the human population, e.g.: Zika, Nipah, H5 Flu
2. **Cross-reactive responses** to pathogens that have not previously entered human population, e.g.: a bat SARS-CoV

Translation to deliverables:

1. Immunogens suitable for vaccine discovery and development
2. Monoclonal antibodies with potential for prevention and therapy
3. Reagent and data resources for early detection and diagnostic assays

Shortened timelines to pandemic-threat countermeasures



Viruses of Interest: Human to Human Transmission

Virus	Order	Family	Genus	Region	Vaccine	mAb	Protein
Lassa virus	Bunyavirales	Arenaviridae	Mammarenavirus	West Africa			Available
Junin	Bunyavirales	Arenaviridae	Mammarenavirus	S. America	Yes		Available
Lujo virus	Bunyavirales	Arenaviridae	Mammarenavirus	Zambia and South Africa			In design
Coronaviruses	Nidovirales	Coronaviridae	Coronaviruses	Global			Available
Andes virus	Bunyavirales	Hantaviridae	Orthohantavirus	S. America	Yes		In design
Hantaan	Bunyavirales	Hantaviridae	Orthohantavirus	Asia, Europe	Yes		In design
Crimean Congo HF	Bunyavirales	Nairoviridae	Orthonairovirus	Europe, Asia, Africa, MENA	Yes		In production
Hazara	Bunyavirales	Nairoviridae	Orthonairovirus	South Asia, MENA			In design
Influenza A, B	Articulavirales	Orthomyxoviridae	Influenzavirus	Global	Yes		Available
Hendra virus	Mononegavirales	Paramyxoviridae	Henipavirus	Australia, Malaysia			In design
Nipah	Mononegavirales	Paramyxoviridae	Henipavirus	Bangladesh, India			Available
Langya	Mononegavirales	Paramyxoviridae	Henipavirus	China			In production
HPIV	Mononegavirales	Paramyxoviridae	Respirovirus	Global			Available
Dabie bandavirus	Bunyavirales	Phenuiviridae	Bandavirus	Asia			In production
Parechovirus 3	Picornavirales	Picornaviridae	Enteroviruses	Global			In design
Coxsackievirus A6, A16	Picornavirales	Picornaviridae	Enteroviruses	Global			In design
Coxsackievirus B2, B3, B4, B5	Picornavirales	Picornaviridae	Enteroviruses	Global			In design
Echovirus 29	Picornavirales	Picornaviridae	Enteroviruses	Global			In design
Echovirus 9, 11, 13, 18, 30	Picornavirales	Picornaviridae	Enteroviruses	Global			In design
Enterovirus C105	Picornavirales	Picornaviridae	Enteroviruses	Global			In design
EV-D68, EV-A71	Picornavirales	Picornaviridae	Enteroviruses	Global	Yes		In production
Rhinovirus	Picornavirales	Picornaviridae	Enteroviruses	Global			In design
Monkeypox	Chitovirales	Poxviridae	Orthopoxvirus	Global	Yes		In production

Viruses of Interest: Zoonotic Transmission

Virus	Order	Family	Genus	Region	Vaccine	mAb	Protein
Machupo virus	Bunyavirales	Arenaviridae	Mammarenavirus	Bolivia, Brazil, Peru			Available
Mopeia virus	Bunyavirales	Arenaviridae	Mammarenavirus	East Africa			Available
Chapare HF	Bunyavirales	Arenaviridae	Mammarenavirus	South America (Bolivia)			In design
Sabiá virus	Bunyavirales	Arenaviridae	Mammarenavirus	South America (Brazil)			In design
Guanarito virus	Bunyavirales	Arenaviridae	Mammarenavirus	South America (Venezuela)			In design
LCMV	Bunyavirales	Arenaviridae	Mammarenavirus	Global			In design
Deltaarterivirus hemfev	Nidovirales	Arteriviridae	Deltaarterivirus	Africa			Available
Borna virus	Mononegavirales	Bornaviridae	Orthobornavirus	Central Europe			In design
Dengue	Amarillovirales	Flaviviridae	Flavivirus	Global	Yes		In design
Murray Valley encephalitis	Amarillovirales	Flaviviridae	Flavivirus	Australia, PNG			In production
Powassan	Amarillovirales	Flaviviridae	Flavivirus	North America, Russia			In design
West Nile	Amarillovirales	Flaviviridae	Flavivirus	Global			Available
Yellow Fever	Amarillovirales	Flaviviridae	Flavivirus	Africa, South America	Yes		In design
Zika	Amarillovirales	Flaviviridae	Flavivirus	Global			Available
Spondweni virus	Amarillovirales	Flaviviridae	Flavivirus	Africa			In design
Dobrava-Belgrade virus	Bunyavirales	Hantaviridae	Orthohantavirus	Russia, Georgia			Available
Laguna Negra virus	Bunyavirales	Hantaviridae	Orthohantavirus	South America			In production
Puumala virus	Bunyavirales	Hantaviridae	Orthohantavirus	Europe, Russia			In design
Seoul Virus	Bunyavirales	Hantaviridae	Orthohantavirus	Global	Yes		In design
Sin Nombre	Bunyavirales	Hantaviridae	Orthohantavirus	North America			In design
Tula virus	Bunyavirales	Hantaviridae	Orthohantavirus	Europe, Asia			In design
Cedar henipavirus	Mononegavirales	Paramyxoviridae	Henipavirus	Australia			In design
Canine distemper	Mononegavirales	Paramyxoviridae	Morbillivirus	Global			In design
Menangle	Mononegavirales	Paramyxoviridae	Paramubulavirus	Australia			In production
Cache Valley virus	Bunyavirales	Peribunyaviridae	Orthobunyavirus	North America			In design
La Crosse virus	Bunyavirales	Peribunyaviridae	Orthobunyavirus	North America			In production
Heartland bandavirus	Bunyavirales	Phenuiviridae	Bandavirus	North America			In design
Punta Toro	Bunyavirales	Phenuiviridae	Phlebovirus	Americas			Available
Rift Valley Fever	Bunyavirales	Phenuiviridae	Phlebovirus	Sub-Saharan Africa			Available
Bat lyssavirus	Mononegavirales	Rhabdoviridae	Lyssavirus	Europe, Australia			In design
Rabies lyssavirus	Mononegavirales	Rhabdoviridae	Lyssavirus	Asia	Yes	Yes	In design
Chandipura vesiculovirus	Mononegavirales	Rhabdoviridae	Vesiculovirus	India, West Africa			In design
Barmah Forest virus	Martellivirales	Togaviridae	Alphavirus	Australia			In design
Ross River virus	Martellivirales	Togaviridae	Alphavirus	Australia, Pacific Islands			In design
Chikungunya	Martellivirales	Togaviridae	Alphavirus	Global			Available
Mayaro virus	Martellivirales	Togaviridae	Alphavirus	Bolivia, Brazil, Peru, Africa			Available
V/E/W EEV	Martellivirales	Togaviridae	Alphavirus	Central and South America			Available

Orthogonal Assay Development

Virus Discovery:

- Shotgun deep sequencing of samples from animal reservoirs and symptomatic humans

Bioinformatics:

- Virus sequence analysis, virus discovery pipeline, serology analysis

PhIP-seq:

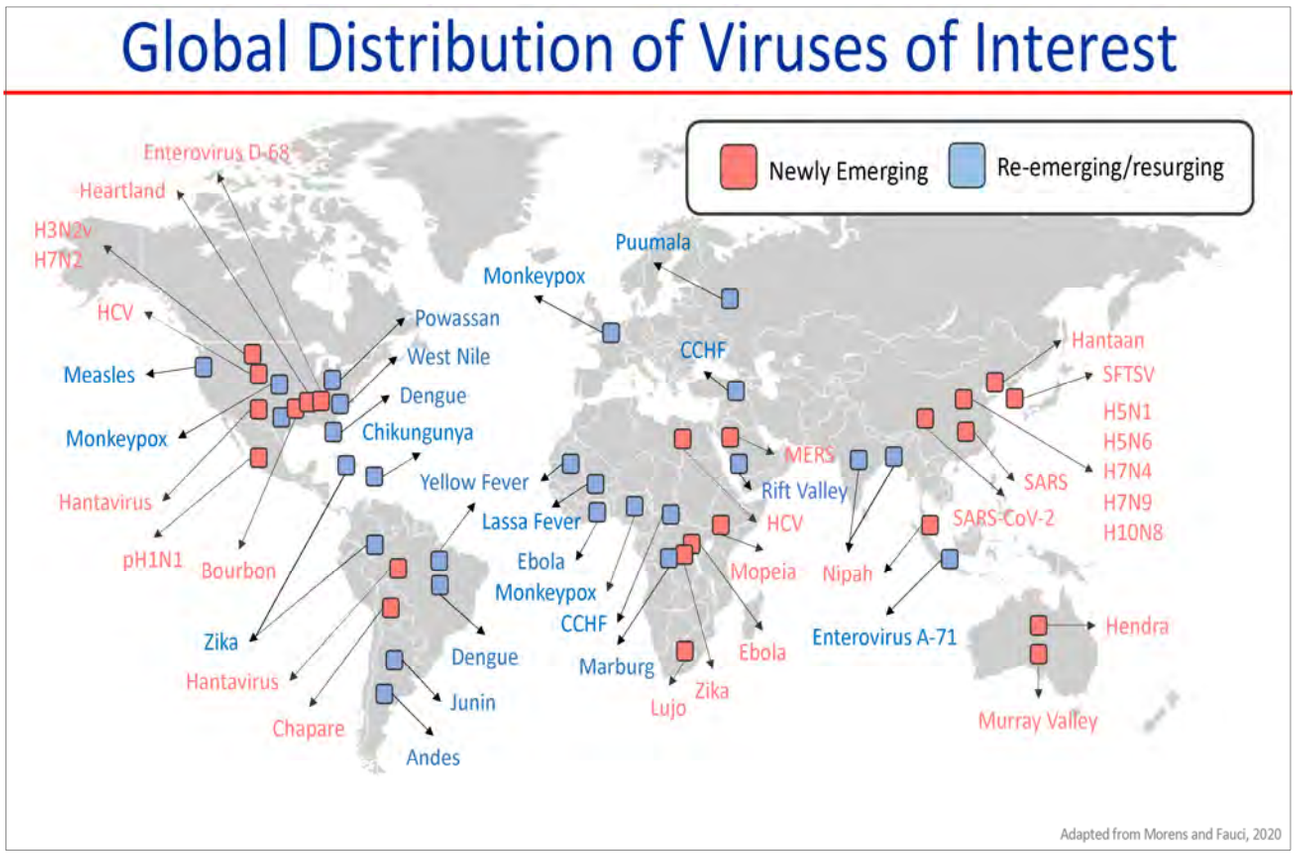
- Phage display, high-throughput, multiplexed, low-specificity serologic assay

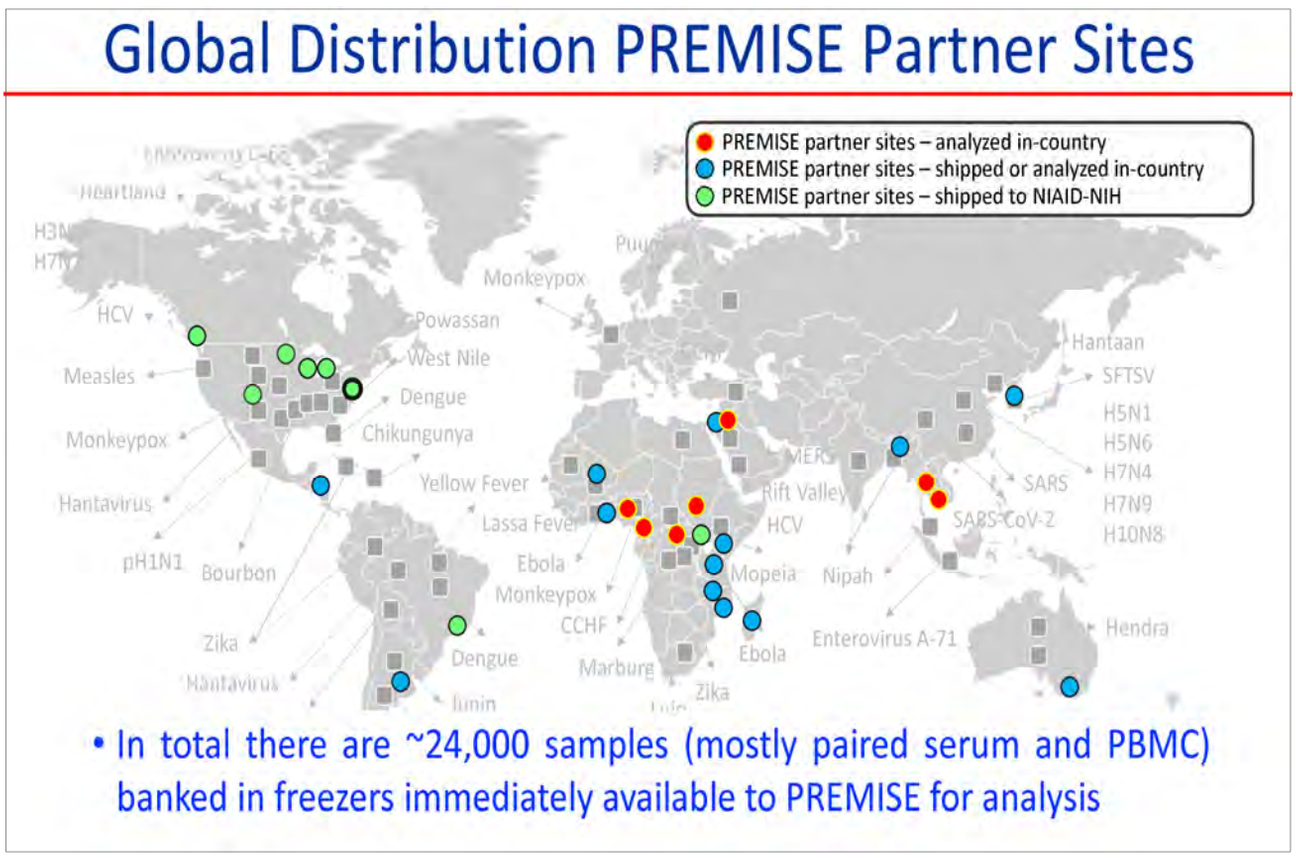
Meso Scale Discovery:

- Multiplexed, high-specificity, electrochemiluminescent serologic assay

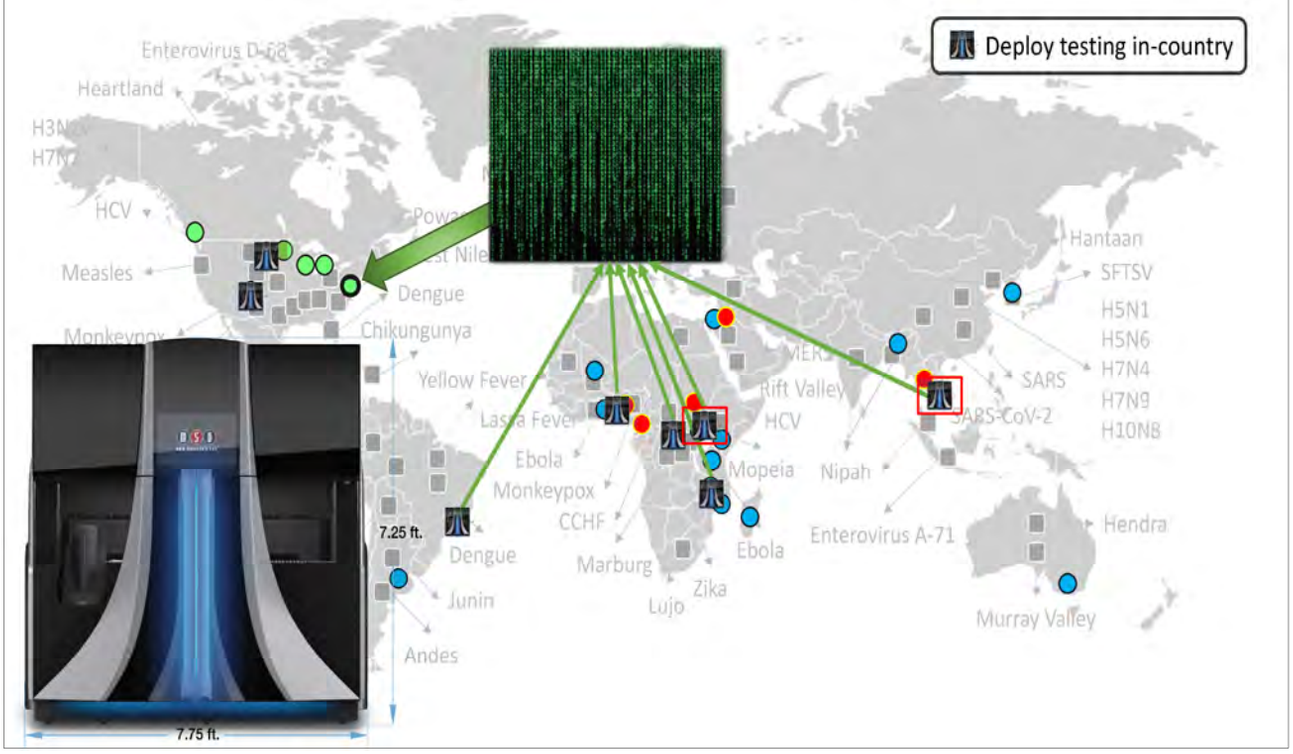
Picodya (Rehovot, Israel):

- Point-of-care automated multiplexed serology


Global Distribution of Viruses of Interest
Newly Emerging
Re-emerging/resurging
Enterovirus D-68
Heartland
H3N2v
H7N2
HCV
Measles
Monkeypox
Hantavirus
pH1N1
Bourbon
Powassan
West Nile
Dengue
Chikungunya
Yellow Fever
Lassa Fever
Ebola
Monkeypox
CCHF
Marburg
Lujo
Zika
Dengue
Junin
Andes
Chapare
Hantavirus
Zika
Puumala
Monkeypox
CCHF
MERS
Rift Valley
HCV
Mopeia
Ebola
Nipah
Enterovirus A-71
Hantaan
SFTSV
H5N1
H5N6
H7N4
H7N9
H10N8
SARS
SARS-CoV-2
Hendra
Murray Valley
Adapted from Morens and Fauci, 2020


Global Distribution PREMISE Partner Sites
PREMISE partner sites – analyzed in-country
PREMISE partner sites – shipped or analyzed in-country
PREMISE partner sites – shipped to NIAID-NIH
• In total there are ~24,000 samples (mostly paired serum and PBMC) banked in freezers immediately available to PREMISE for analysis

In-Country Capability: MSD PARSEC Network



MSD Plate Assay Strategy

Childhood Respiratory Panel (EV-D68 Study)

Assay	Virus	Status	Virus Group	Receptor	Spread
1	EV-D68	Ready	Enterovirus/Picorna	ICAM5	Respiratory
2	EV-71	Ready	Enterovirus/Picorna	SCARB2	Fecal-oral
3	hMPV	Ready	Meta/Pneumo	Sialic Acid	Respiratory
4	RSV (DSCav)	Ready	Orthopneumo/Pneumo	NCL	Respiratory
5	Influenza A and B	Ready	Orthomyxo	Sialic Acid	Respiratory
6	Rhinovirus C	In production	Enterovirus/Picorna	CDHR3	Respiratory
7	CoV-2 D614G BA.5	Ready	Sarbecovirus/Corona	ACE2	Respiratory
8	hPIV (I-IV)	Ready	Paramyxo	Sialic Acid	Respiratory
9	Parechovirus A3	In production	Picorna	FcRn/β2M	Fecal/Oral
10	La Crosse (control)	Ready	Ortho/PeriBunya	CLRs/CME	Mosquito

Regional Panel 1 (Africa and Middle East)

Assay	Virus	Status	Virus Group	Receptor	Spread
1	Rift Valley	In design	Phlebovirus/Phenui	LRP1	Livestock
2	Mopeia	In production	Mammarena/Arena	αDG	Rodent
3	RABLV, IKOV, MOKV	In design	Lyssa/Rhabdov	nAChR	Animal Saliva
4	Lassa virus	In production	Mammarena/Arena	αDG	Rodent
5	Spondweni	In design	Flavivirus	AXL/TIM/Tyro/CLR	Mosquito
6	MERS	Ready	Merbeco	DPP4	Respiratory
7	Ebola	In design	Filoviridae	TIM/CLR/NPC1	Bat/Human
8	Lujo	In design	Mammarena/Arena	αDG; NRP2	Rodent
9	Crimean Congo	In production	Orthonairo/Nairo	NCL/CME	Tick
10	Marburg	In design	Filoviridae	TIM/Tyro/CLR	Bat/Human

Regional Panel 2 (Asia and Australia)

Assay	Virus	Status	Virus Group	Receptor	Spread
1	Nipah/Hendra	Ready/In design	Henipa/Paramyxo	Ephrin B2/3	Bat/Pig/Human
2	SFTSV (Dabie)	In production	Bandavirus/Phenui	TBD	Tick/Human
3	Hazara	In design	Orthonairo/Nairo	NCL/CME	Tick
4	LCMV and Seoul	In design	Arena/Hanta	αDG/Integrins	Rodent
5	Hantaan	In design	Orthohanta/Hanta	β1–3 Integrin, DAF/CD55, gC1qR	Rodent
6	Ross River and Murray V.	In design	Alphavirus/Toga	Heparin	Mosquito
7	CoV-1 and MERS	Ready	Sarbeco/Merbeco	ACE2/DPP4	Respiratory
8	Chandipura	In design	Vesicula/Rhabdo	Vimentin	Sandflies
9	Japanese and Tick-Borne Encephalitis	In design	Flavivirus	PLVAP/GKN3/TIM/CLR/LBP/Int.	Mosquito/Tick
10	RABLV, IKOV, MOKV	In design	Lyssa/Rhabdov	nAChR	Animal Saliva

Regional Panel 3 (Latin America)

Assay	Virus	Status	Virus Group	Receptor	Spread
1	Junin	Ready	Mammarena/Arena	TfR1	Rodent
2	Zika	In production	Flavivirus	AXL/TIM/Tyro/CLR	Mosquito
3	Yellow Fever Virus	In design	Flavivirus	HSP70/GAG/CLR	Mosquito
4	West Nile Virus	In design	Flavivirus	MR/CLR	Mosquito
5	RABLV, IKOV, MOKV	In design	Lyssa/Rhabdov	nAChR	Animal Saliva
6	Chikungunya	Ready	Alphavirus/Toga	AXL/TIM/MXRA8	Mosquito
7	Dengue (Type IV)	In production	Flavivirus	MR/CLR	Mosquito
8	Mayaro	In design	Alphavirus/Toga	MXRA8	Mosquito
9	Bunya virus group 1: Machupo, Sabia, Chapare, Guanarito	In design	Mammarena/Arena	TfR1	Rodent
10	Bunya virus group 2: Andes, Laguna Negra	In design	Orthohanta/Hanta	β1–3 Integrin, DAF/CD55, gC1qR	Rodent

- Proteins designed by PREMISE, made by: VRC, MSD, U. Mich, GenScript, Gingko

Current Partnerships

Collaboration	National and International Site	Contact	Mechanism	Nature of Partnership
NIAID with International Sites				
DMID/CREID	Senegal, Pakistan, Taiwan	Jean Patterson	Collaboration	Serology and PBMC assays from multiple CREID cohorts
DAIDS/TREAT Asia	Thailand	Carlie Williams, Annette Sohn	MTA	Serology and PBMC assays from multiple HIV cohorts
DIR/LVD	--	Ted Pierson	Collaboration	Flavivirus vaccine and mAb discovery
DIR/LMVR	Cambodia	Jessica Manning	Collaboration	Flavivirus vaccine and mAb discovery
DIR/RML	Ghana, Bangladesh	Vincent Munster	MTA	Serology and virus discovery
Office of Data Science and Emerging Technologies	--	Wilbert van Panhuis	Collaboration	Data storage, use and access
Other US-based with International Sites				
WRAIR	Jordan, Thailand, Nigeria, Kenya, Uganda, Tanzania	Nelson Michael	MTA	Serology and PBMC assays and international PREMISE sites
Princeton University	South Sudan	Julien Ayroles	RCA	Serology and PBMC assays
Yale University and Broad Institute	New Haven, Connecticut; Cambridge, Massachusetts	Craig Wilen, John Doench	RCA, contract	Virus receptor discovery
University of Chicago	Madagascar	Cara Brook	MTA	Virus discovery
Harvard University	Madagascar	Chris Golden	RCA	Virus discovery
Zoo New England	Madagascar	Eric Baitchman, Rachel Johnston	RCA	Virus discovery
University of Michigan	Ann Arbor, Michigan	Jeanne Stuckey	Contract	Protein production
International				
G42 Healthcare and Abu Dhabi Department of Health	United Arab Emirates	Mohamed Sayegh (via NIAID/OD)	RCA	International PREMISE site
National Institute of Human Viral Diseases	Pergamino, Argentina	María de los Ángeles Conti	RCA	International PREMISE site (Hantaan and Junin virus)
Korea National Institute of Infectious Diseases	Seoul, South Korea	Dokeun Kim	RCA	International PREMISE site (Dabie bandavirus/SFTSV)
Duke-NUS Medical School	Singapore	Linfa Wang	RCA	International PREMISE site (Langyavirus)
Sheba Medical Center and Ministry of Health	Israel	Gili Regev-Yochai	RCA	International PREMISE site
University of Washington and Aga Khan University	Pakistan	Najeeha Iqbal/Wes Van Voohries	RCA	International PREMISE site
EV-D68 pilot study				
University of Colorado	Denver, Colorado	Kevin Messacar	RCA	Clinical site (Funded by VRC)
University of North Carolina at Chapel Hill	Chapel Hill, North Carolina	Matthew Vogt	RCA	Clinical site (Funded by VRC)
Weill Cornell Medical Center	New York, New York	Sallie Permar, Perdita Permaul	RCA	Clinical site (Funded by VRC)
University of Alabama at Birmingham	Birmingham, Alabama	David Kimberlin	RCA	Clinical site (Funded by DMID)
Princeton University	Princeton, New Jersey	Bryan Grenfell, Jessica Metcalf	RCA	Epidemiology
National Library of Medicine				
NCBI	--	Aravind Iyer	Collaboration	Comprehensive pathogen database project
Industry				
Meso Scale Discovery	Gaithersburg, Maryland	Jim Wilbur	RCA	Serologic assay development
Picodya	Israel	Uri Keler	RCA	Serologic assay development
Gingko	Boston, MA		RCA	Protein production

Current Overall Status

- 5 full-time PREMISE staff
- 29 active collaborations with government, academia and industry
  - 11 RCAs executed, 5 under review, 2 being drafted
  - 9 international collaborators
- Official NIAID CREID external stakeholder
- 8,395 serum samples at VRC
- 82 viruses of interest on our main list — of those:
  - 62 PhIP-seq libraries have been designed and produced for serology
  - 23 conformationally intact viral proteins (monomers, dimers, trimers, VLPs) designed, produced and are ready for serology, B cell probes, immunogens
- New virus discovery bioinformatic pipeline to be uploaded to publicly available NIAID data ecosystem website

Current Specific Project Status

- Partnership with CDC to develop MPXV-specific serologic assay
- nAb against Langya virus in collaboration with Duke NU Singapore
- nAb against Junín in collaboration with Argentine Maiztegui NHVDI
- nAb against SFTSV in collaboration with Kyung-Chang Kim (Center for Emerging Virus Research, KNIID)
- Sheba Medical Center pandemic preparedness institute established under NIH-Israel Ministry of Health MOU
  - Coronaviruses, flaviviruses, influenza
- USAID MERC grant submitted for VRC-Sheba-al Quds collaborative project on Hajj serosurveillance
- Partnership with BMGF to train LMIC sites in rapid assembly, transfection and production of mAbs
- 6 national and 4 international teams trained in mAb discovery pipeline:
  - University of the Witwatersrand, South Africa
  - Sheba Medical Center, Israel
  - Duke-National University Singapore
  - Imperial College, London, UK

How PREMISE Engages with Partners

- PREMISE can provide:
  - Design of and training for in-country assay and analysis capability
  - Virus discovery, serosurveillance, mAb discovery, immunogen design and analytics
  - PREMISE discoveries and resources are transferable
- Partners can provide:
  - Research partners and in-country study sites
  - Samples from human cohorts and zoonotic reservoirs
  - Capability to further develop therapeutic countermeasures
- PREMISE cannot provide:
  - Funding
  - An ongoing supply of assay kits, consumables, clinical grade products etc...

2. Development of therapeutic human monoclonal antibodies against SFTSV infection

Dr. Han-saem Lee(NIID, Korea)

Han-saem Lee

Ph.D. Staff scientist

National Institute of Infectious Diseases, Korea National Institute of Health

- **EDUCATION:**

2005 ~ 2008	Ph.D. of Medical Science Ulsan University, Medical school, Seoul, Korea
2001 ~ 2003	Master of Science in Life Science Sogang University, Seoul, Korea
1996 ~ 2000	Bachelor of Science in Life Science Sogang University, Seoul, Korea

- **PROFESSIONAL EXPERIENCE:**

2016 ~ Present	Staff Scientist Division of Emerging Infectious Virus and Vector Research, KNIH, Chungbuk, Korea (PI: Dr. Kim, Kyoung Chang, Dr. Lee, Joo-Yeon) Study: MERS-CoV, SARS-CoV-2, SFTSV, and Nipah virus
2010 ~ 2015	Senior Researcher Division of Respiratory Viruses KNIH, Chungbuk, Korea (PI: Dr. Kim, Kisoon, Dr. Kim, Sungsoon) Study: baculovirus, RSV, Measles, MERS-CoV
2009 ~ 2010	Research fellow Molecular Virology, Mayo Clinic, Minnesota, USA (PI: Dr. Peng, Kah whey) Study: Recombinant Measles vector for cancer gene therapy
2008 ~ 2009	Post-doc Medical science, Ulsan University, Medical school (PI: Dr, Lee, Huiran)

• PROFESSIONAL EXPERIENCE:

	Study: Recombinant Adeno-Associated Viral vector for cancer gene therapy
2003 ~ 2004	Research scientist
	Chongkeundang(종근당) Pharmaceutical CO. LTD., Korea
	Study: new drug discovery for cancer, PDE inhibitors, and diabetes treatment

• SUMMARY

Topic: Development of therapeutic antibodies against MERS-CoV and SFTSV

Abstract

Neutralizing antibodies protect against viral infection efficiently by interfering with virions that bind to receptors, blocking virus entry into cells, resulting prevention of virus propagation and spread. The development of human monoclonal neutralizing antibodies has increased for therapeutic or prophylactic use against newly emerging infectious diseases.

The outbreak of MERS occurred in the Republic of Korea in 2015. Although high mortality (~35%) by MERS infection has been reported worldwide, unfortunately, there is currently no specific vaccine or treatment for MERS-CoV infection. In this study, we present seven human monoclonal antibodies (mAbs) isolated from peripheral blood mononuclear cells of convalescent Korean MERS patients. The mAbs specifically bind to MERS-CoV spike protein S1 and RBD. The plaque reduction neutralization test was performed to quantify the neutralizing activity of the antibody against the virus. Out of 24 candidates, six antibodies are found to neutralize MERS-CoV infection efficiently. We also evaluated antibody affinity based on enzyme-linked immunosorbent assay and surface plasmon resonance using S1 antigen. We also elucidated the interaction of KNIH90-F1 with RBD of spike protein by X-ray chrystallography.

Severe fever with thrombocytopenia syndrome virus (SFTSV), named Dabies virus, is an emerging fatal hemorrhagic fever virus with fatality of upto 30% in Asia, especially China, Korea and Japan, belongs bunyavirus. In this study, we also found human monoclonal antibodies targeting SFTSV Gn and Gc surface glycoproteins to develop therapeutic monoclonal antibodies. This research is still being proceeded.

Topic: Development of the novel Tuberculosis vaccine applied to various platforms in Korea

Abstract

Tuberculosis (TB) is the second leading infectious cause of mortality worldwide, with about two million deaths yearly. Globally in 2020, an estimated 5.8 million incident cases were caused by M. tuberculosis. Moreover, there are an estimated 1.3 million deaths from TB. South Korea ranked the highest TB incidence among the Organization for Economic Cooperation and Development (OECD) members. The only licensed vaccine, Mycobacterium bovis Bacillus Calmette Guerin (BCG), is effective in infants and adolescents. Unfortunately, the varying immune efficacy and short duration cause limited protection effects, so the BCG vaccine does not protect all generation groups from tuberculosis. Although significant progress in the search for a more effective TB vaccine has been demonstrated over the last two decades, there is still no replacement for the licensed BCG vaccine. Since 2018, the Korean government has implemented the "Midterm strategies to strengthen TB prevention and management" based on the 2nd National Strategic Plan for Tuberculosis Control (2018-2022). The program includes a strategy to support the development of a new tuberculosis vaccine. In this session, we would like to introduce the developing status of the new tuberculosis vaccine using various platforms and new formulation, in Korea.

Development of therapeutic human monoclonal antibodies against SFTSV infection

22. Feb. 2023.
NIID, KNIH
Emerging Virus Research Center
Emerging Virus and Vector Research
Dr. Hansaem Lee

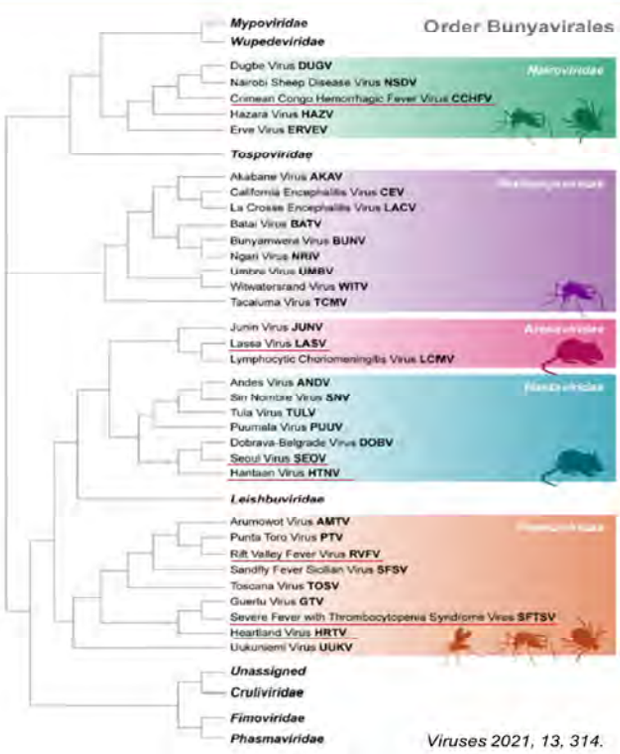
Overview

1. Background
2. Human monoclonal anti-SFTSV Gc antibodies
3. Human monoclonal anti-SFTSV Gn antibodies
4. Summary

Backgrounds

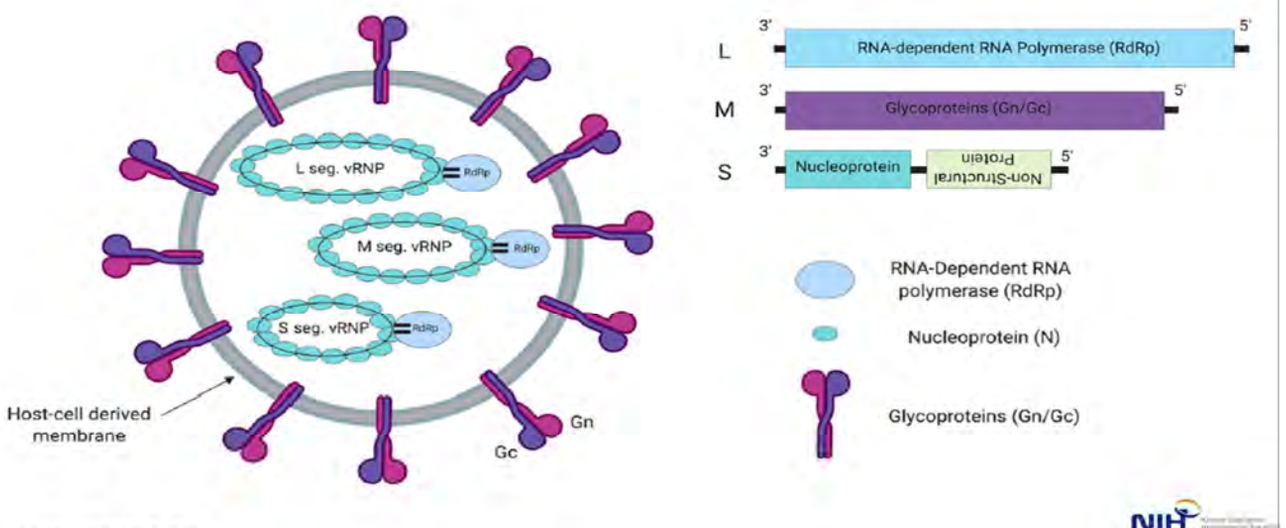
Virus

- **Severe fever with thrombocytopenia syndrome (SFTS) caused by a tick-born virus named *Dabie bandavirus***
- **Family *Phenuiviridae*, order *Bunyavirales***



Virus

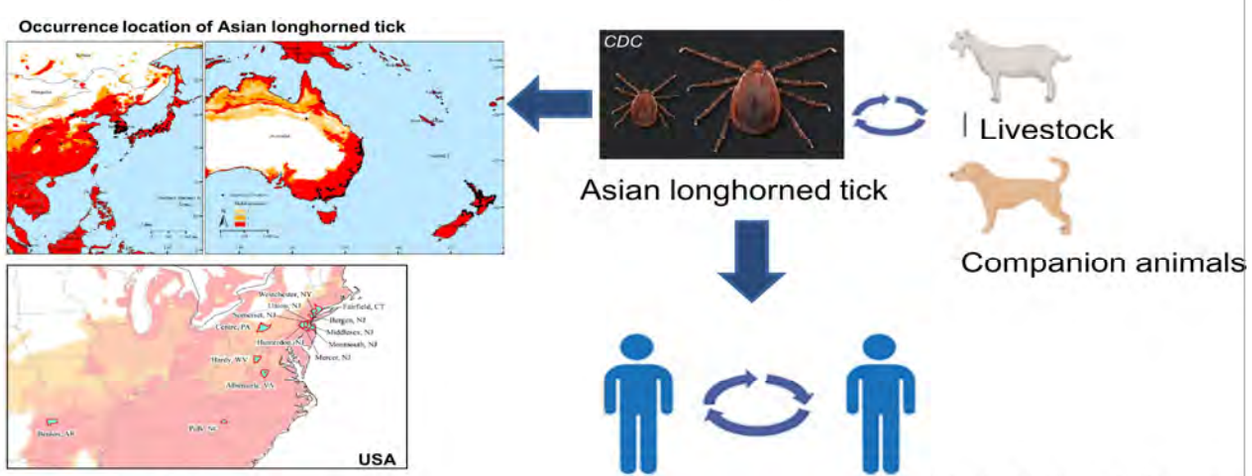
- **a segmented, negative-strand RNA virus genome**
- **Large (L), medium (M), and small (S) segments**



Vaccines 2019, 7, 125

Transmission

- SFTSV transmitted by *Haemaphysalis longicornis* (Asian longhorned tick)
- SFTSV is found in a wide range of wild and domestic animals
- Human to human transmission through direct contact



Scientific Report (2019) 9:498

Infect Dis Ther (2022) 11:1805–1819

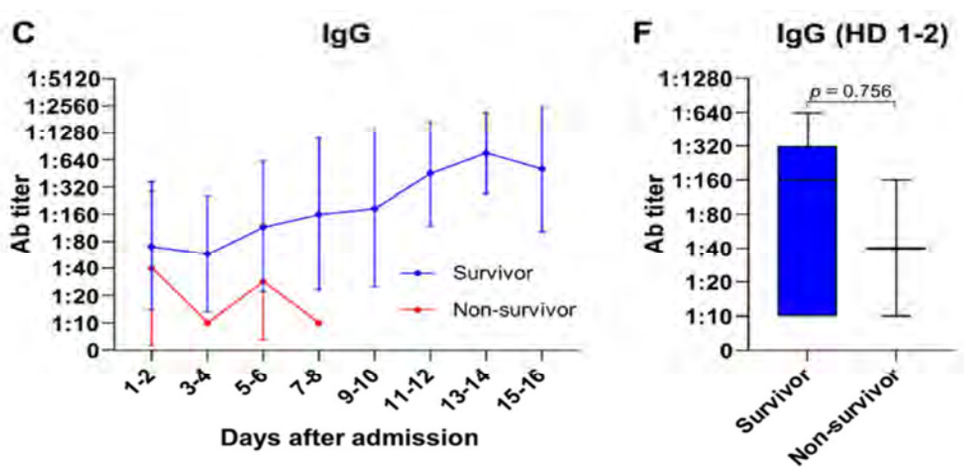
SFTS prevalence

- SFTSV was first reported in China in 2009
- Japan and Korea (2012)
- Vietnam (2019), Taiwan (2020)
- Fatality (7~27%) from 2010 to 2018
  - Japan 27%, South Korea 20%, China 7%

2010-~2018	China	Japan	South Korea
SFTS cases	11,995	396	866
Annual incidence/10^5	0.1	0.04	0.19
No. of deaths	881	107	173
Fatality rate (%)	7.34	27.02	19.98
Age median	62 (52-70)	74 (5-96)	65 (64-66)
% of female cases	53.15	51.52	50.35
Major epidemic seasons	May-July	May-July	July, September-October

Clinical symptoms of SFTS

- High fever and thrombocytopenia
- Diarrhea, headache, myalgia, leukocytopenia
- Severe multiorgan failure
- Asymptomatic SFTS infection
- Non-survivors did not develop SFTSV IgGs



Viruses 2021, 13, 2351

SFTSV vaccine development

- No vaccine approved

Nucleotides

- **DNA (KAIST, South Korea)**
  - Glycoproteins (Gn-Gc)
  - N, NSs, RdRp
- **mRNA** (KNIH-Moderna)

Protein (Subunit)

- **NSs (China)**
  - no clearance of SFTSV
- **Gn, Gc, Gn-Gc (KNIH)**

Virus-like particles

- **VLP-SFTSV (KNIH)**

Viral vectors

- **rVSV-SFTSV Gn/Gc** (CAS, China)
- rVAC m8-N, Gn/Gc

Inactivated or Live-attenuated

- **Inactivated SFTSV HB29 (China)**
- **Inactivated SFTSV B2 (KNIH)**
- **rHB2912aaNSs and rHB29NSsP102A (NS mutant)**

SFTSV therapy studies

	In vitro			*In vivo*				
Agent	**Virus strain**	**IC_{50} (μM)**	**References**	**Animal**	**Dose mg/kg/day**	**Dose of virus**	**Survival (%)**	**References**
Ribavirin	Korean isolate	15.1-35.7	Lee et al. 2017	STAT2-/- hamster	75 (twice)	50 PFU	0	Gowen et al. 2017
	Japanese isolate	40.1	Baba et al. 2017	IFNAR-/- C57BL/6	25 (once)	10^6 TCID50	70	Tani et al. 2016
	HB29	49.7	Smee et al. 2018		100 (once)	10^6 TCID50	66	
Favipiravir	SPLO10	6	Tani et al. 2016	IFNAR-/- C57BL/6	60 (once)	10^6 TCID50	100	Tani et al. 2016
	Japanese isolate	25	Baba et al. 2017		120(twice)	10^6 TCID50	100	Tani et al. 2018
					100(twice)	3 PFU	90	Smee et al. 2018
				STAT2-/- hamster	300(twice)	50 PFU	100	Gowen et al. 2017
					150(twice)	50 PFU	100	
Benidipine	Chinese isolate	1.4	Li et al. 2019	C57BL/6 mouse	15 (once)	10^5 TCID50	100	Li et al. 2019
				humanized mouse	15 (once)	10^5 TCID50	83.3	
Nifedipine	Chinese isolate	98	Li et al. 2019	C57BL/6 mouse	100 (once)	10^5 TCID50	100	Li et al. 2019
				humanized mouse	100 (once)	10^5 TCID50	100	
2'-Fluoro-2'-deoxycytidine	HB29	3.7	Smee et al. 2018	IFNAR-/- C57BL/6	50 (twice)	3 PFU	80	Smee et al. 2018
					100(twice)		100	
					200(twice)		80	
IFNgamma	SPLO30	IC90 12 U/mL	Shimojima et al.2015	3 days old ICR	0.5 ug (once)	1.5x10^3 TCID50	0-25	Ning et al. 2019
					0.05 ug (once)	1.5x10^3 TCID50	0-25	

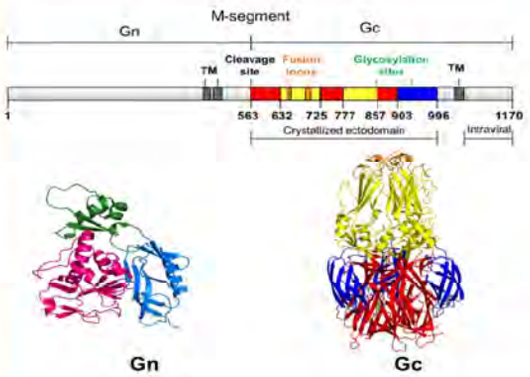
SFTSV neutralizing antibodies

Antibody name	Type (target antigen)	Effects			References
		In vitro	In vivo	Clinical trial	
MAb4-5	Human monoclonal (SFTSV-Gn)	EC90: 1.8 uM - Vero cell - (Ag) Gn domain III		-	X. Guo et al., Clinical and Vaccine Immunology, 2013 Yan Wu et al., PNAS, 2017
Ab10	Human monoclonal (SFTSV-Gn)	Y318,EC90: 55.6 nM - Vero cell - (Ag) Gn domain II	- A129 mouse, - 600ug/day x 4 days	-	Kim KH et al PLOS pathogen (2019)
SNB02	Nanobody (SFTSV-Gn)	EC50: 2.7 ug/mL - Vero-E6 - (Ag) sGn-Fc	- NCG-HuPBL mouse - 400ug/day x 4 days	-	Wu X et al. JCI Insight, 2020

Human monoclonal anti-SFTSV Gc antibodies

Gn and Gc glycoproteins of SFTSV

SFTSV Glycoproteins



- Attachment to host receptors
- Neutralizing antibodies
- Dimer

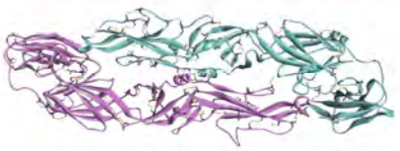
- Fusion to cell membrane
- Endocytosis
- Monomer, trimer

Host receptors

- **DC-SIGN (C-type lectin)**
  - Dendritic-cell specific intercellular adhesion molecule 3-grabbing nonintegrin
  - SFTSV, RVFV, TOSV, Uukuniemi virus, HIV, SARS-CoV, CMV
  - Cis-, Trans- infection
  - Endocytosis
- **L-SIGN (C-type lectin)**
  - 77% homology of DC-SIGN
  - SFTSV, SARS-CoV-2
- **NMMHC-IIA**
  - Non-muscle myosin heavy chain II A
  - SFTSV, HSV-1

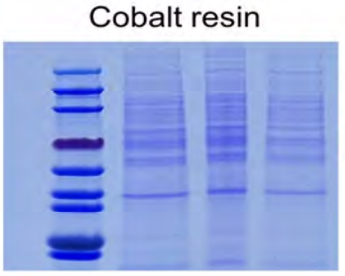
Human antibodies against SFTSV Gc

Gc glycoprotein of SFTSV

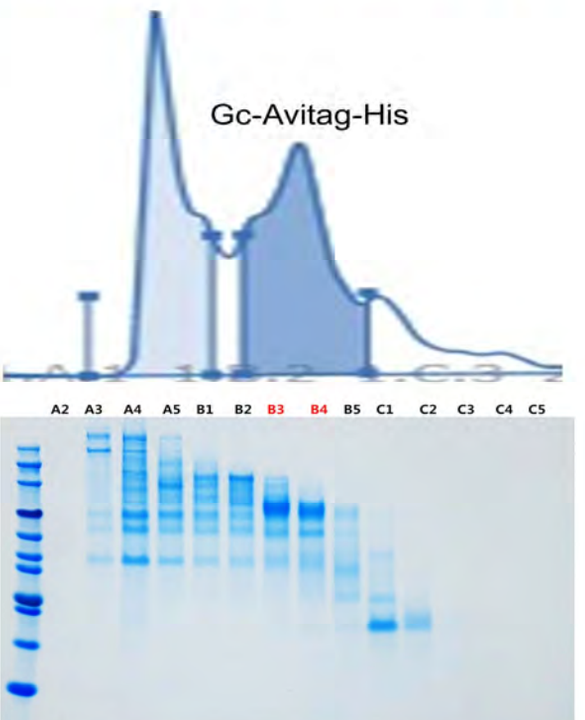


Gc dimer

Cobalt resin



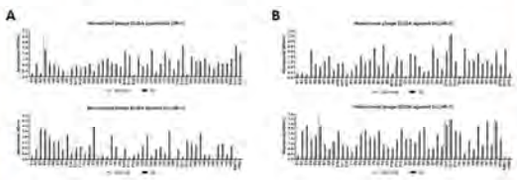
SEC



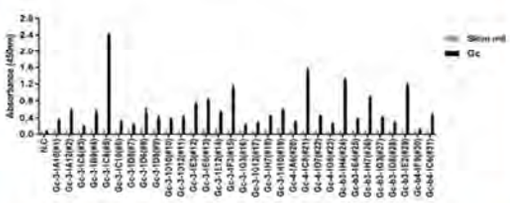
Human antibodies against SFTSV Gc

Screening SFTSV Gc-specific clones

Antibody phage display library

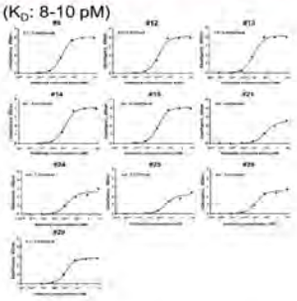


Fab ELISA
unique antibody gene analysis

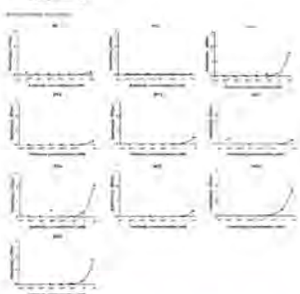


ELISA with 10 Anti-SFTSV IgGs

SFTSV Gc (K_D: 8-10 pM)



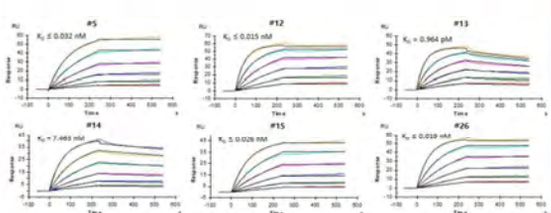
RVFV Gc



High affinity and specificity

Human antibodies against SFTSV Gc

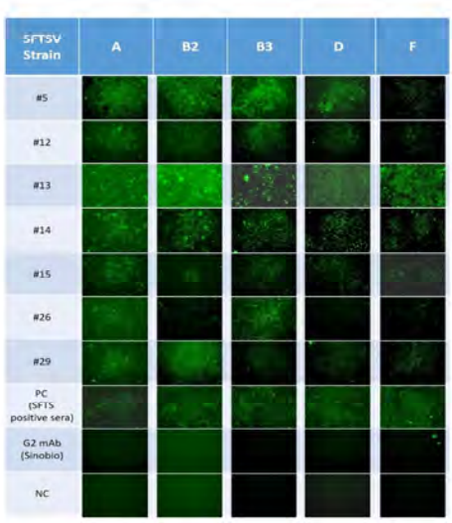
Affinity analysis in SPR assays



Ligand	Analyte	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	Chi² (RU²)
SFTSV Gc-His	#5	$3.125x10^5$	$\leq 1.000x10^{-4}$	$\leq 3.200x10^{-11}$	60.8	0.8
	#12	$6.820x10^5$	$\leq 1.000x10^{-4}$	$\leq 1.466x10^{-11}$	56.5	1.7
	#13	$7.588x10^5$	$7.313x10^{-4}$	$9.638x10^{-10}$	44.2	1.1
	#14	$5.608x10^4$	$4.185x10^{-4}$	$7.463x10^{-9}$	39.8	0.4
	#15	$3.800x10^5$	$\leq 1.000x10^{-4}$	$\leq 2.632x10^{-11}$	45.2	0.4
	#26	$5.250x10^5$	$\leq 1.000x10^{-4}$	$\leq 1.905x10^{-11}$	53.9	0.8

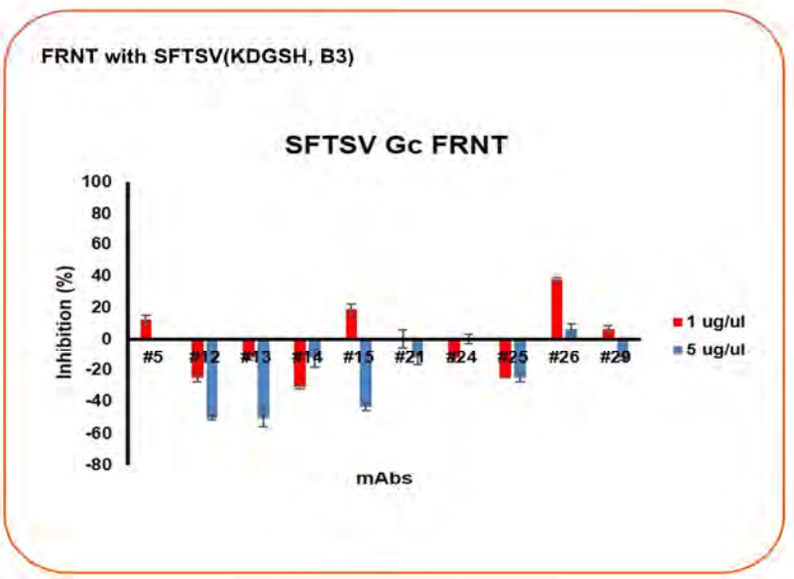
High affinities to SFTSV Gc at pM levels

Broad range of SFTSV genotypes



Anti-SFTSV Gc IgGs for SFTSV diagnostics (patent application)

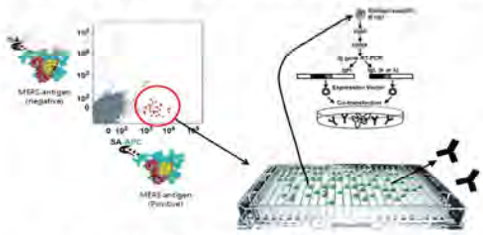
Human antibodies against SFTSV Gc



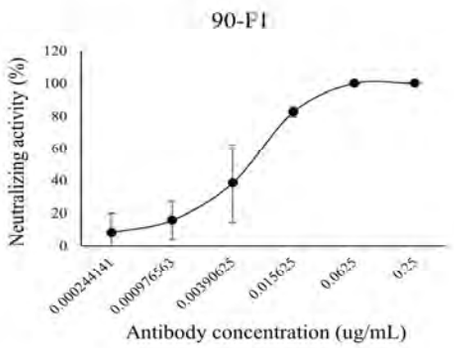
Human monoclonal anti-SFTSV Gn antibodies

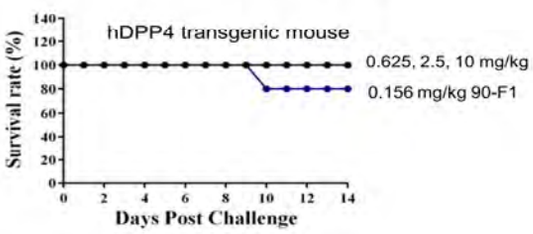
Rapid antibody technology

MERS-CoV Neutralizing antibodies
from the collaboration with Vaccine Research Center of NIH

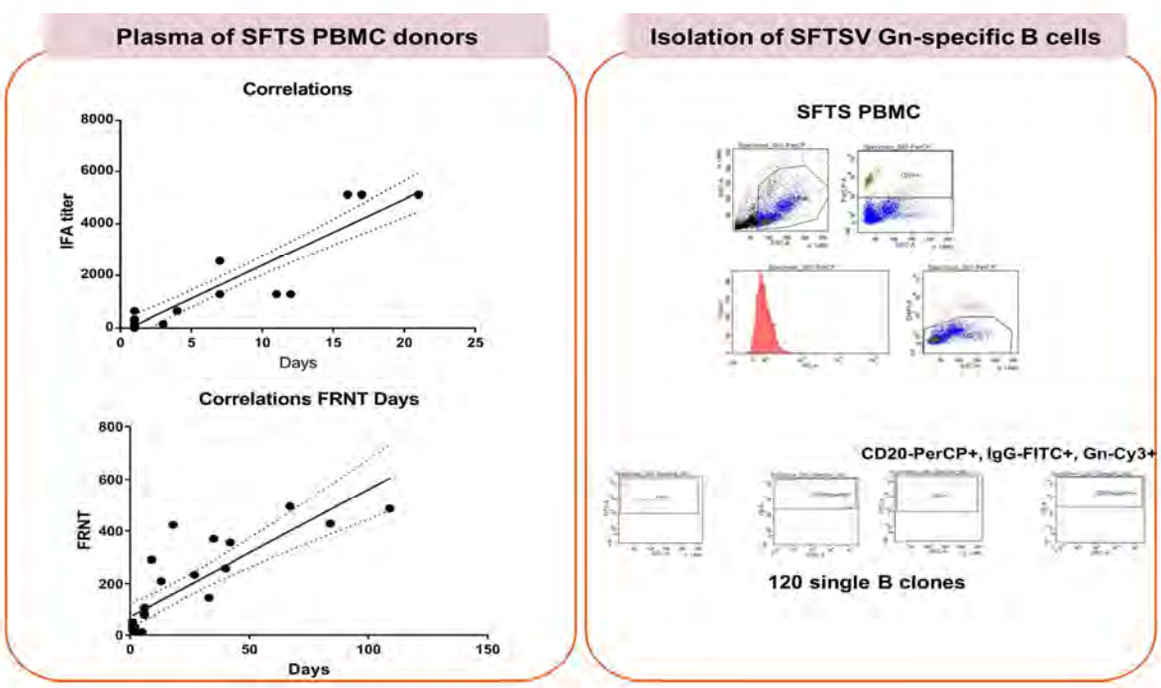


Isolation of single B cells containing
monoclonal antibody by using antigen probes



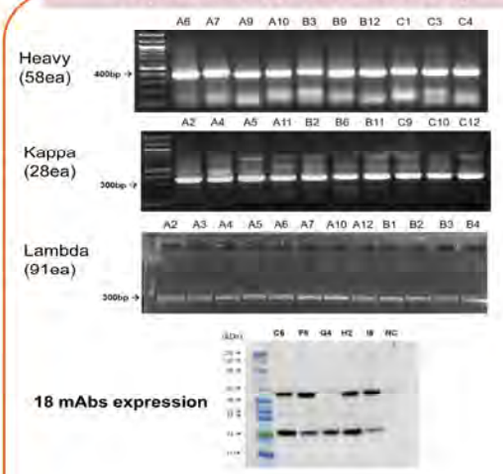


B cells from SFTS convalescent donors

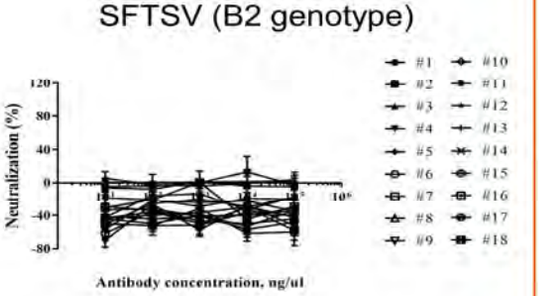


Human antibodies against SFTSV Gn by rapid antibody technology

Expression of SFTSV Gn antibody



FRNT of SFTSV Gn antibodies

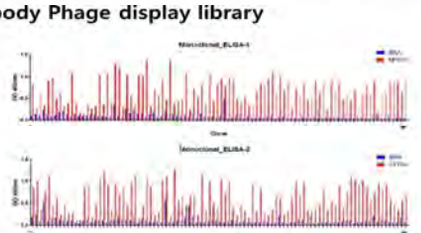


No neutralizing activity

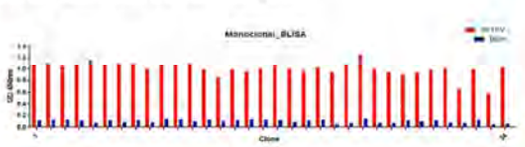
Human antibodies against SFTSV Gn by antibody phage display system

Screening of SFTSV Gn-specific antibodies

Antibody Phage display library

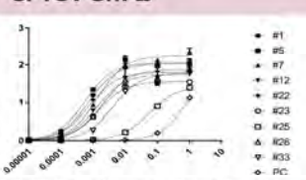


ELISA with SFTSV Gn antigen



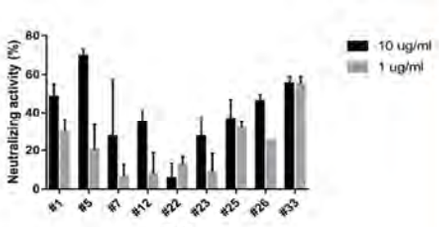
SFTSV Gn Ab

SFTSV Gn ELISA

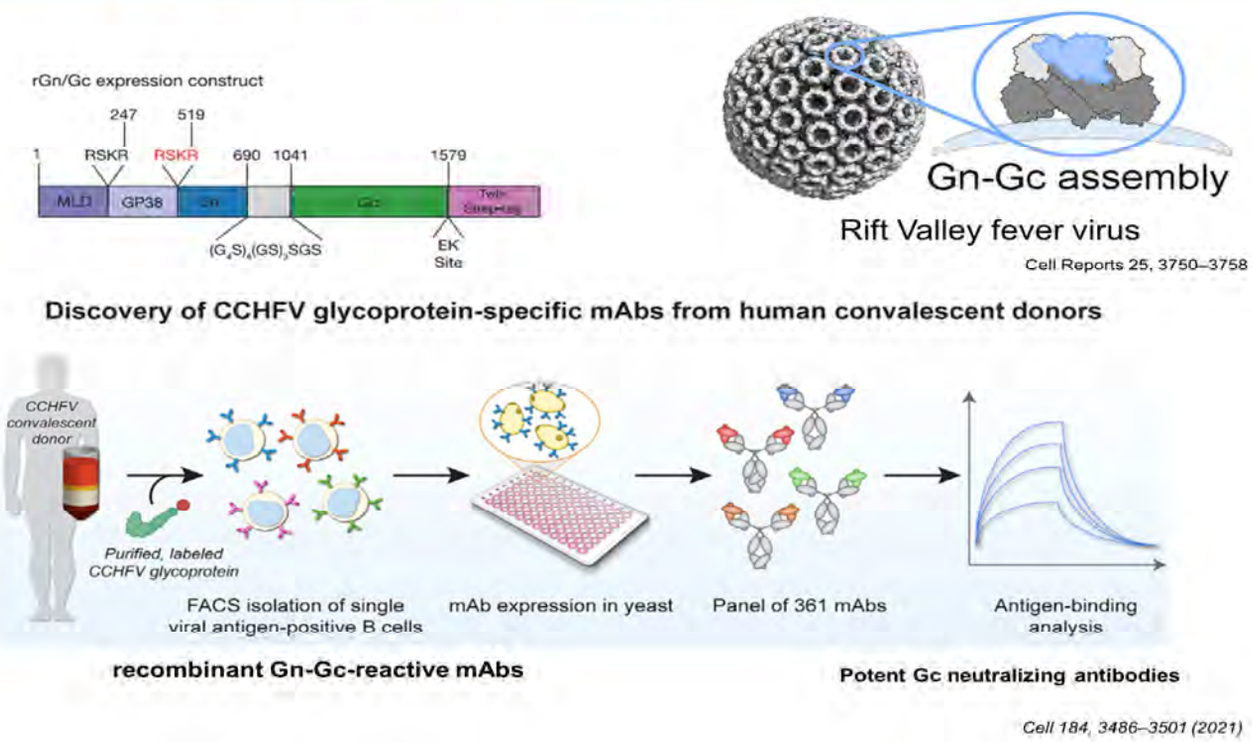


	#1	#5	#7	#12	#22	#23	#25	#26	#33
Vmax	2.033	2.061	2.245	1.749	1.805	1.558	1.438	1.882	1.777
Km	7.40E-04	5.58E-04	1.39E-03	1.31E-03	7.36E-04	1.40E-03	5.62E-02	1.92E-03	4.15E-03
K_D (pM)	49.3	37.2	92.8	87.1	49.1	93.4	3750	128	277

SFTSV FRNT



Need to design SFTSV antigens for nAb probes



Summary

- Gn- or Gc-specific antibodies by antibody phage display system and rapid antibody technology have affinities but no neutralizing activities.
- Immunization with the combination of Gn and Gc induced neutralizing antibodies in the mouse model.
- Designing SFTSV antigen probes is required for the development of SFTSV vaccination as well as the potent neutralizing antibodies.
- The studies with Gn- and Gc-specific B cells will proceed further.

KNIH for SFTSV research team
Dr. Joo-Yeon Lee
Dr. Hee-young Lim
Dr. So-Young Lee
Pyoung-Hwa Jeon
Da-Sol Kim
Na-Young Kim
Jae-Hun Jeong
Thank you!
NATIONAL INSTITUTES OF HEALTH
U.S NIH/NIAID/VRC
PREMISE
KBIOHEALTH
SKAI
스크립스코리아항체연구원
Scripps Korea Antibody Institute
서울아산병원
Asan Medical Center
NIH

Part 2. Phage therapy for bacterial infectious diseases

Chair:
Myoung-don Oh, M.D., PhD.

1. Bacteriophages and Endolysins Combating Multidrug Resistant (MDR) Pathogens
Dr. Hee-joon Myung (LyseNTech, Korea)

2. NIH-Supported Clinical Trial of Phage Therapy for Cystic Fibrosis Begins
Dr. Dennis Dixon (NIAID, USA)

Part 2. Phage therapy for bacterial infectious diseases

Moderator

Myoung-don OH

Professor

Seoul National University College of Medicine

- **EDUCATION:**

1992 ~ 1994	SNU, PhD
1977 ~ 1983	Seoul National University (SNU) College of Medicine, M.D.

- **PROFESSIONAL EXPERIENCE:**

1997 ~ Present	Professor, SNU College of Medicine
1992 ~ Present	Professor, Division of Infectious Diseases, SNU Hospital
2020 ~ Present	Chair, National Committee of Clinical Management of Infectious Diseases
2009 ~ 2011	President, Korea Society of Infectious Diseases
2022. 1 ~ 4	Member, Transition Team for the 20th President of KOREA

Part 2

Phage therapy for bacterial infectious diseases

1. Bacteriophages and Endolysins Combating Multidrug Resistant (MDR) Pathogens

Dr. Hee-joon Myung (LyseNTech, Korea)

Hee-joon Myung

Professor, Founder and CEO

Hankuk University of Foreign Studies, LyseNTech

- **EDUCATION:**

1987 ~ 1992	Ph. D. Microbiology. University of Illinois-Urbana/Champaign
1983 ~ 1987	BS. Microbiology. Seoul National University

- **PROFESSIONAL EXPERIENCE:**

2021 ~ Present	Associate editor, Frontiers in Microbiology
2019 ~ Present	Founder and CEO, LyseNTech
2010 ~ Present	Director, The Bacteriophage Bank of Korea
1994 ~ Present	Professor, Hankuk University of Foreign Studies
1993 ~ 1994	Postdoc, University of California-Berkeley

- **SUMMARY**

Topic: Bacteriophages and Endolysins Combating Multidrug Resistant (MDR) Pathogens

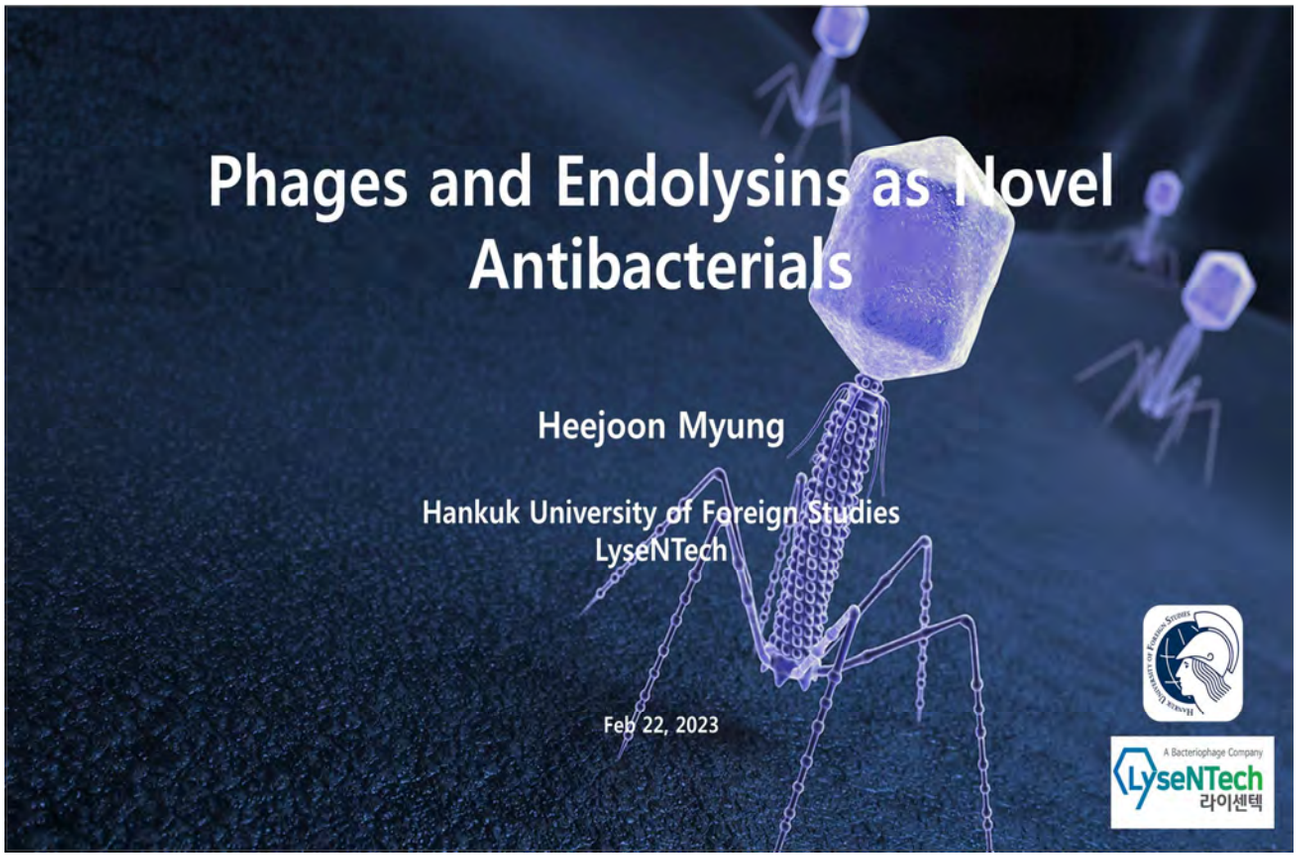
Abstract

Rapidly growing antibiotic resistance is posing a great threat to human health. It was reported that 4.95 million deaths were related to antimicrobial resistance in 2019. Covid-19 worsened the situation of misuse/overuse of antibiotics due to standard prescription of antibiotic to patients. But pipeline for development of new antibiotics is almost dried out. Bacteriophages are viruses infecting bacteria. Endolysins are phage-encoded, cell wall-degrading enzymes needed when progeny phages burst out from inside host bacteria. If externally supplied as recombinant proteins, they can kill the bacteria. Accordingly, bacteriophages and endolysins are increasingly spotlighted as modalities for combatting MDR pathogens. Successful clinical trial cases of phage therapy have been reported from Western world as well as from some East European countries. Development of endolysins as recombinant protein drugs is under way. Current phage therapy and endolysin therapy in various animal models and human clinical cases will be presented.

Topic: Development of the novel Tuberculosis vaccine applied to various platforms in Korea

Abstract

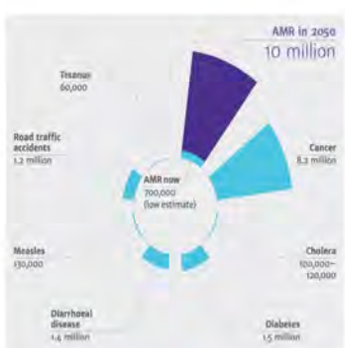
Tuberculosis (TB) is the second leading infectious cause of mortality worldwide, with about two million deaths yearly. Globally in 2020, an estimated 5.8 million incident cases were caused by M. tuberculosis. Moreover, there are an estimated 1.3 million deaths from TB. South Korea ranked the highest TB incidence among the Organization for Economic Cooperation and Development (OECD) members. The only licensed vaccine, Mycobacterium bovis Bacillus Calmette Guerin (BCG), is effective in infants and adolescents. Unfortunately, the varying immune efficacy and short duration cause limited protection effects, so the BCG vaccine does not protect all generation groups from tuberculosis. Although significant progress in the search for a more effective TB vaccine has been demonstrated over the last two decades, there is still no replacement for the licensed BCG vaccine. Since 2018, the Korean government has implemented the "Midterm strategies to strengthen TB prevention and management" based on the 2nd National Strategic Plan for Tuberculosis Control (2018-2022). The program includes a strategy to support the development of a new tuberculosis vaccine. In this session, we would like to introduce the developing status of the new tuberculosis vaccine using various platforms and new formulation, in Korea.



1. Antibiotic Crisis

(C. L. Ventola, 2015. P&T)

- Rapid appearance of resistant mutant pathogen after introduction of a novel antibiotic discouraged big pharma from developing new antibiotics



(J. O'Neill, 2014. AMR review)

- 10 million deaths expected related to antimicrobial resistance in 2050, which would surpass the number of deaths due to cancer

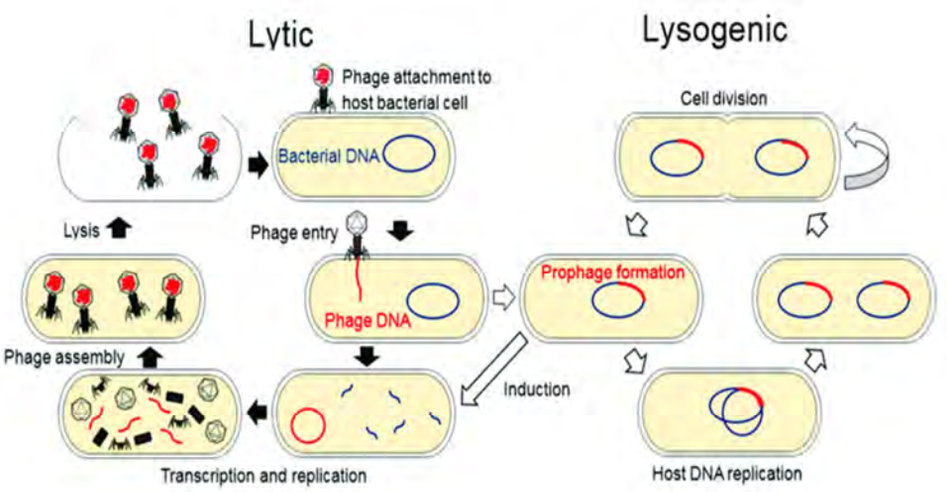
(Antimicrobial Resistance Collaborators, 2022)

- In 2019, 4.95 million deaths related to AMR was already reported.

2. Introduction to Bacteriophages (Phages)

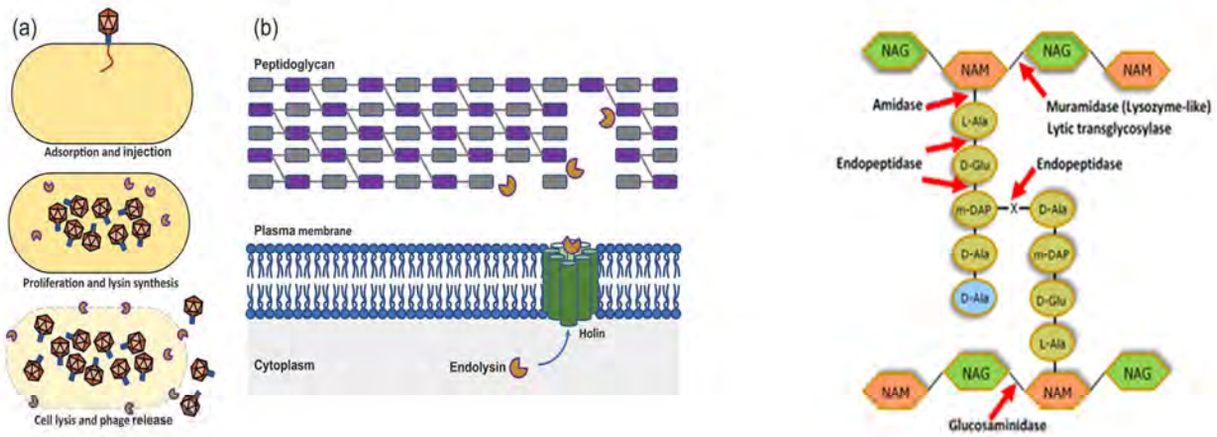
- Viruses infecting bacterial hosts
- Most abundant and diverse biological entities on earth
- Lysogenic or lytic life cycle
- Present in environment, plants, and animals including human
- Maintenance of bacterial balance in nature

Bacteriophage life cycle



(S. Batinovic et al. 2019. Pathogens)

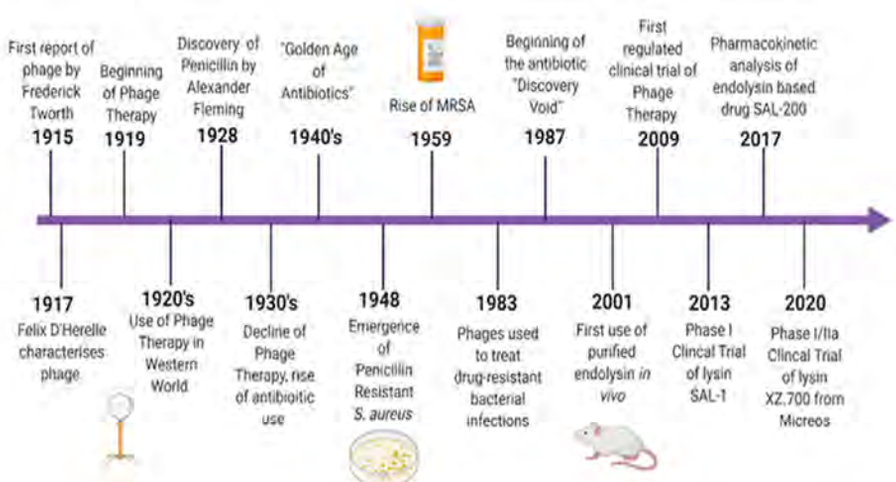
Bacteriophage Endolysin



(Mondal et al. 2020)

(Sao Jose et al. 2018)

3. History of Phage Therapy



(E. Murray et al. 2021. Viruses)

1st Regulated clinical trial of bacteriophage therapy

A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant *Pseudomonas aeruginosa*; a preliminary report of efficacy

Wright, A.*, Hawkins, C.H.†, Änggård, E.E.† & Harper, D.R.†

*UCL Ear Institute and Royal National Throat, Nose and Ear Hospital, Grays Inn Road, London, and †Biocontrol Limited, BioCity, Pennyfoot Street, Nottingham, UK

Accepted for publication 29 April 2009
Clin. Otolaryngol. 2009, 34, 349–357

Objectives: To evaluate the efficacy and safety of a therapeutic bacteriophage preparation (Biophage-PA) targeting antibiotic-resistant *Pseudomonas aeruginosa* in chronic *otitis*.

Design: Randomised, double-blind, placebo-controlled Phase I/II clinical trial approved by UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Central Office for Research Ethics Committees (COREC) ethical review process.

Setting: A single specialist university hospital.

Participants: 24 patients with chronic otitis with a duration of several years (2–58). Each patient had, at the time of entry to the trial, an ear infection because of an antibiotic-resistant *P. aeruginosa* strain sensitive to one or more of the six phages present in Biophage-PA. Participants were randomised in two groups of 12 treated with either a single dose of Biophage-PA or placebo and followed up at 7, 21 and 42 days after treatment by the same otologist. Ears were thoroughly cleaned on each occasion and clinical and microbiological indicators measured.

Main outcome measures: Physician assessed erythema/inflammation, ulceration/granulation/polyps, discharge quantity, discharge type and odour using a Visual Analogue Scale (VAS). Patients reported discomfort, itchiness, wetness and smell also using a VAS. Bacterial levels of *P. aeruginosa* and phage counts from swabs were measured initially and at follow-up. At each visit patients were asked about side effects using a structured form. Digital otoscopic images were obtained on days 0 and 42 for illustrative purposes only.

Results: Relative to day 0, pooled patient- and physician-reported clinical indicators improved for the phage treated group relative to the placebo group. Variation from baseline levels was statistically significant for combined data from all clinic days only for the phage treated group. Variation from baseline levels was statistically significant for the majority of the patient assessed clinical indicators only for the phage treated group. *P. aeruginosa* counts were significantly lower only in the phage treated group. No treatment related adverse event was reported.

Conclusion: The first controlled clinical trial of a therapeutic bacteriophage preparation showed efficacy and safety in chronic *otitis* because of chemo-resistant *P. aeruginosa*.

(Wright A et al. 2019. Clinical Otolaryngology)

- Performed in UK (David Harper)
- 24 chronic otitis patients with chemo-resistant *P. aeruginosa* infection
- Clinical indicators improved for the phage treated group relative to the placebo group
- *P. aeruginosa* count were significantly lower in the phage treated group
- No treatment related adverse event

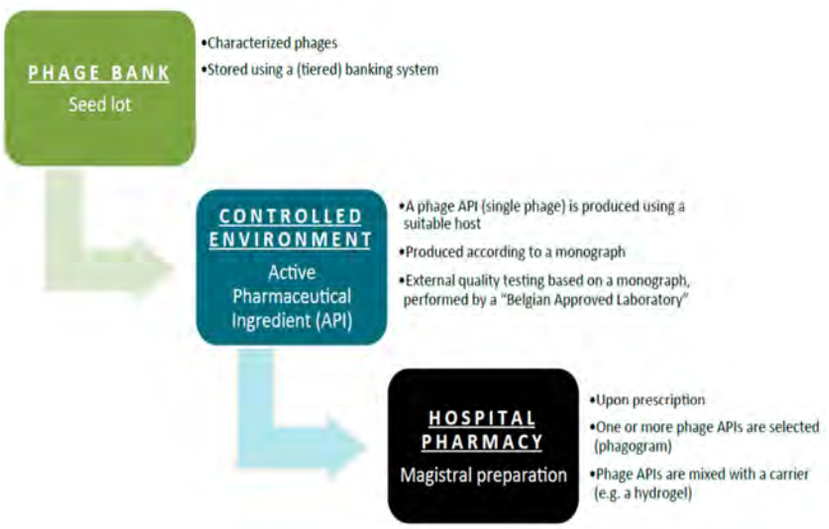
4. Phage Therapy (PT) Centers Today

4. Phage Therapy Centers
1) Eliava Phage Therapy Center in Georgia

ELIAVA Phage Therapy Center

- Part of Eliava Institute Bacteriophages, Microbiology, and Virology
- Clinical phage therapy for 100 years
- Local or distance treatments
- Lacks documentation needed for approval by US FDA or EMA

4. Phage Therapy Centers
2) Queen Astrid Military Hospital in Belgium



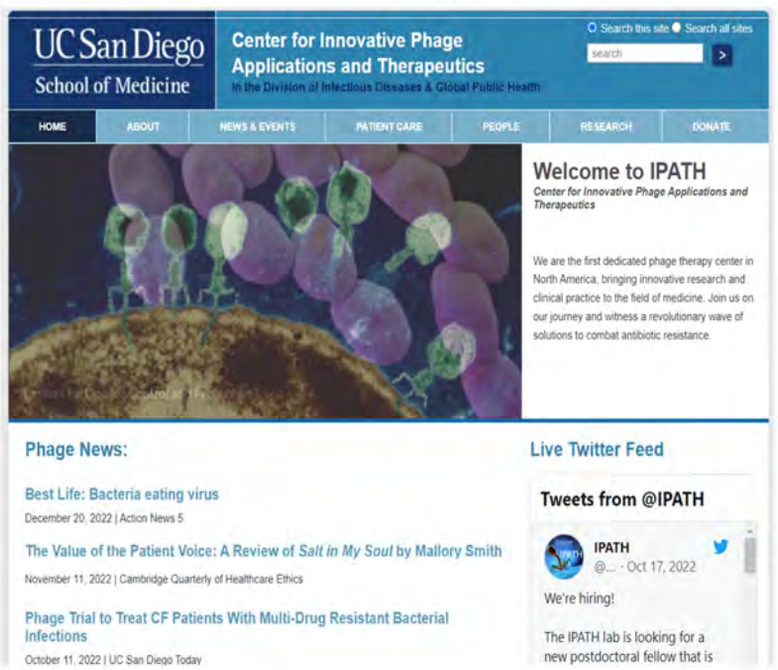
- Preparation and production of personalized phage cocktail in a facility
- Under Magistral Phage framework, GMP has not been required for phage therapy in Belgium since 2018.
- ca 110 patients have been treated as of 2022

<Magistral phage medicine process.>

(Pirnay J-P et al. 2018 *Viruses)*

4. Phage Therapy Centers
3) iPATH at UCSD

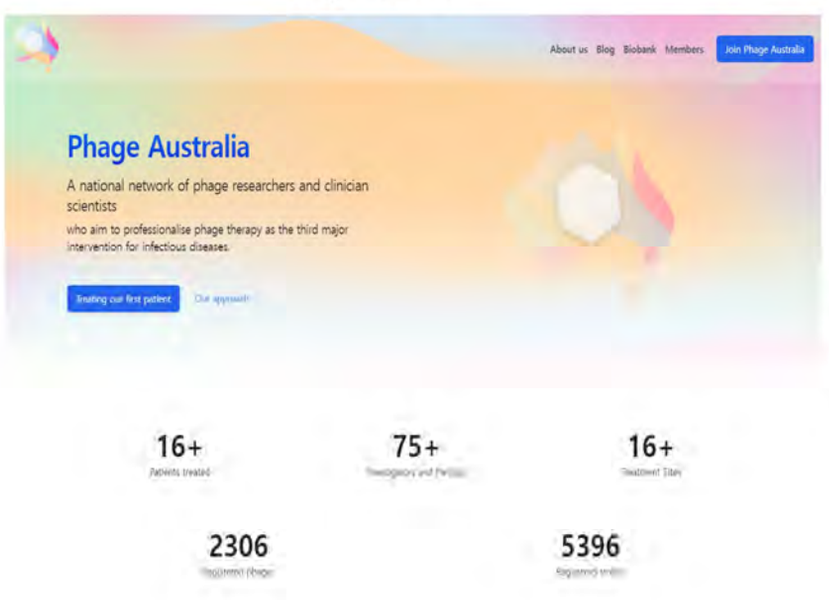
iPATH (Center for Innovative Phage Application and Therapeutics)



- Founded in 2018
- UC-San Diego
- Directors Robert Schooley and Steffanie Strathdee
- eIND-based phage therapy

4. Phage Therapy Centers
4) Phage Australia

Phage Australia



- A nationwide clinical phage therapy trial in Australia
- Started in 2021
- 16 clinical centers participating
- Led by Jon Iredell in Sydney Medical School

4. Phage Therapy Centers
5) Phage UK

Phage UK

UK PHAGE THERAPY

Delivering phage therapy for the United Kingdom

ABOUT US | NEWS | ABOUT PHAGE THERAPY | CONTACT US

About us

What is UK Phage Therapy?

UK Phage Therapy is a non-profit initiative which has been operating informally since 2020 and was officially formed as a company in July 2022.

UKPT will be the UK's specialist clinical phage centre, bringing together phage manufacturing, research and development and clinical provision.

Working with industrial partners, and with strong international links, we will manufacture

- An initiative operating from 2022
- Clinical trials for NHS patients
- Director Josh Jones

5. A Famous Phage Therapy Case

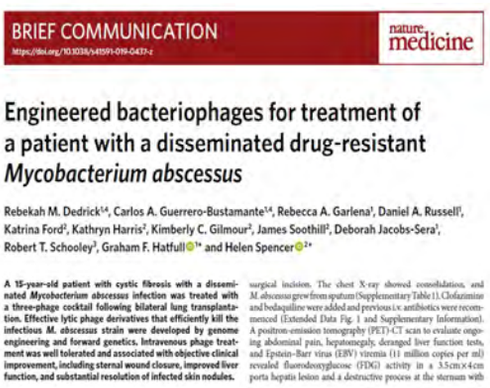
Antimicrobial Agents and Chemotherapy

EXPERIMENTAL THERAPEUTICS

Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection

- Steffanie Strathdee and Tom Patterson of UCSD
- Tom was infected with PDR *A. baumannii* during the couple's trip to Egypt
- Steffanie tried to save dying husband with old solution-bacteriophages
- Phages were collected from US Navy, AmpliPhi, and Texas A&M
- A phage cocktail was prepared and administered by Robert Schooley
- Tom recovered from coma
- Tom was discharged from the hospital in one month

6. Clinical Phage Therapy Cases in Journal Articles
(1) 2019 *M. abscessus*


BRIEF COMMUNICATION
nature medicine

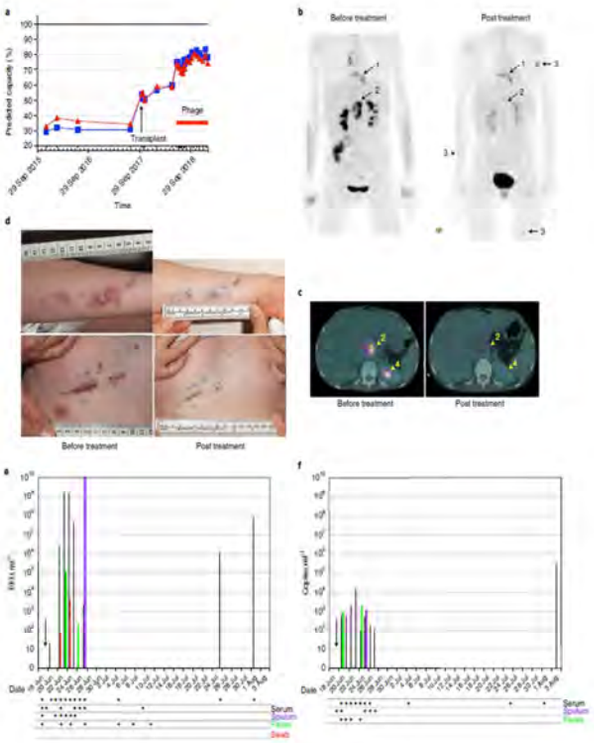
Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*

Rebekah M. Dedrick[1,4], Carlos A. Guerrero-Bustamante[1,4], Rebecca A. Garlena[1], Daniel A. Russell[1], Katrina Ford[2], Kathryn Harris[2], Kimberly C. Gilmour[2], James Soothill[2], Deborah Jacobs-Sera[1], Robert T. Schooley[3], Graham F. Hatfull[1*] and Helen Spencer[2*]

A 15-year-old patient with cystic fibrosis with a disseminated *Mycobacterium abscessus* infection was treated with a three-phage cocktail following bilateral lung transplantation. Effective lytic phage derivatives that efficiently kill the infectious *M. abscessus* strain were developed by genome engineering and forward genetics. Intravenous phage treatment was well tolerated and associated with objective clinical improvement, including sternal wound closure, improved liver function, and substantial resolution of infected skin nodules.

surgical incision. The chest X-ray showed consolidation, and *M. abscessus* grew from sputum (Supplementary Table 1). Clofazimine and bedaquiline were added and previous i.v. antibiotics were recommenced (Extended Data Fig. 1 and Supplementary Information). A positron-emission tomography (PET)-CT scan to evaluate ongoing abdominal pain, hepatomegaly, deranged liver function tests, and Epstein–Barr virus (EBV) viremia (11 million copies per ml) revealed fluorodeoxyglucose (FDG) activity in a 3.5 cm × 4 cm porta hepatis lesion and a destructive process at the sternum with

- 15 yo cystic fibrosis patient
- 3 phages cocktail (one engineered), IV administration
- Clinical improvement, including sternal wound closure, improved liver function, and substantial resolution of infected skin nodules



6. Clinical Phage Therapy Cases in Journal Articles
(2) 2021 *M. abscessus*

nature medicine
BRIEF COMMUNICATION

Potent antibody-mediated neutralization limits bacteriophage treatment of a pulmonary *Mycobacterium abscessus* infection

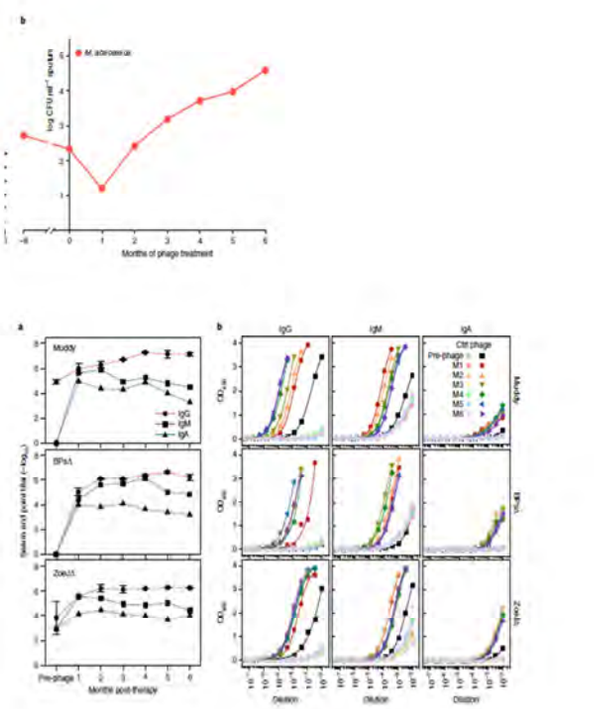
Rebekah M. Dedrick[1,6], Krista G. Freeman[1,6], Jan A. Nguyen[2,6], Asli Bahadirli-Talbott[2], Bailey E. Smith[1], Andrew E. Wu[2], Aaron S. Ong[3], Cheng Ting Lin[3], Lisa C. Ruppel[4], Nicole M. Parrish[5], Graham F. Hatfull[1✉] and Keira A. Cohen[2✉]

An 81-year-old immunocompetent patient with bronchiectasis and refractory *Mycobacterium abscessus* lung disease was treated for 6 months with a three-phage cocktail active against the strain. In this case study of phage to lower infectious burden, intravenous administration was safe and reduced the *M. abscessus* sputum load tenfold within one month. However, after two months, *M. abscessus* counts increased as the patient mounted a robust IgM- and IgG-mediated neutralizing antibody response to the phages, which was associated with limited therapeutic efficacy.

the patient infected with GD01 (ref. [7]). Muddy and the engineered BPsΔ33HTH_HRM10 and Zoe1Δ45 (ref. [7]) (hereafter referred to as BPsΔ and Zoe1Δ, respectively) each were shown to effectively kill strain GD02 in vitro (Fig. 1d). Although potently bactericidal, a few surviving colonies were recovered after challenge of 10^8 colony forming units (CFUs) of bacteria with phages; rescreening showed several patterns of resistance but no derivative was resistant to all three phages (Extended Data Fig. 4).

A three-phage cocktail was prepared from high titer, highly purified preparations and shown to be endotoxin-free and sterile,

- 81 yo immunocompetent patient with bronchiectasis
- 3 phages cocktail (one engineered), IV administration
- Reduced *M. abscessus* burden tenfold within 1 month
- After 2 months, bacterial burden increased due to increasing IGG and IgM neutralizing antibodies
- Only limited therapeutic efficacy



6. Clinical Phage Therapy Cases in Journal Articles

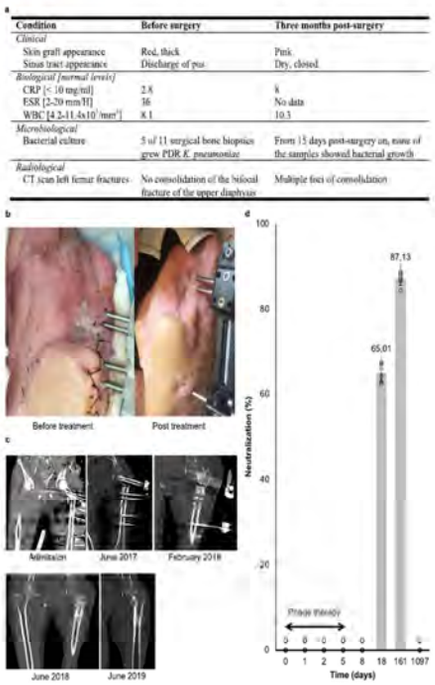
(3) 2022 *K. pneumoniae*

ARTICLE

Combination of pre-adapted bacteriophage therapy and antibiotics for treatment of fracture-related infection due to pandrug-resistant *Klebsiella pneumoniae*

Anais Eskenazi[1,9✉], Cédric Lood[2,3], Julia Wubbolts[4], Maya Hites[1], Nana Balarjishvili[5], Lika Leshkasheli[5], Lia Askilashvili[5], Leila Kvachadze[5], Vera van Noort[3,6], Jeroen Wagemans[2], Marc Jayankura[7], Nina Chanishvili[5], Mark de Boer[4], Peter Nibbering[4], Mzia Kutateladze[5], Rob Lavigne[2], Maya Merabishvili[8] & Jean-Paul Pirnay[8]

A 30-year-old bombing victim with a fracture-related pandrug-resistant *Klebsiella pneumoniae* infection after long-term (>700 days) antibiotic therapy is treated with a pre-adapted bacteriophage along with meropenem and colistin, followed by ceftazidime/avibactam. This salvage therapy results in objective clinical, microbiological and radiological improvement of the patient's wounds and overall condition. In support, the bacteriophage and antibiotic combination is highly effective against the patient's *K. pneumoniae* strain *in vitro*, in 7-day mature biofilms and in suspensions.



Condition	Before surgery	Three months post-surgery
Clinical		
Skin graft appearance	Red, thick	Pink
Sinus tract appearance	Discharge of pus	Dry, closed
Biological [normal levels]		
CRP [< 10 mg/ml]	2.8	8
ESR [2-20 mm/H]	36	No data
WBC [4.2-11.4x10^3/mm^3]	8.1	10.3
Microbiological		
Bacterial culture	5 of 11 surgical bone biopsies grew PDR *K. pneumoniae*	From 15 days post-surgery on, none of the samples showed bacterial growth
Radiological		
CT scan left femur fractures	No consolidation of the bifocal fracture of the upper diaphysis	Multiple foci of consolidation

- 30 yo bombing victim
- Fracture-related *K. pneumoniae* infection
- Pre-adapted single phage + meropenem/colistin/ceftazidime/avibactam treatment
- Objective clinical, microbiological and radiological improvement of the patient's wounds and overall condition
- The bacteriophage and antibiotic combination is highly effective against the patient's *K. pneumoniae* strain *in vitro*, in 7-day mature biofilms and in suspensions

6. Clinical Phage Therapy Cases in Journal Articles

(4) 2022 *M. abscessus*

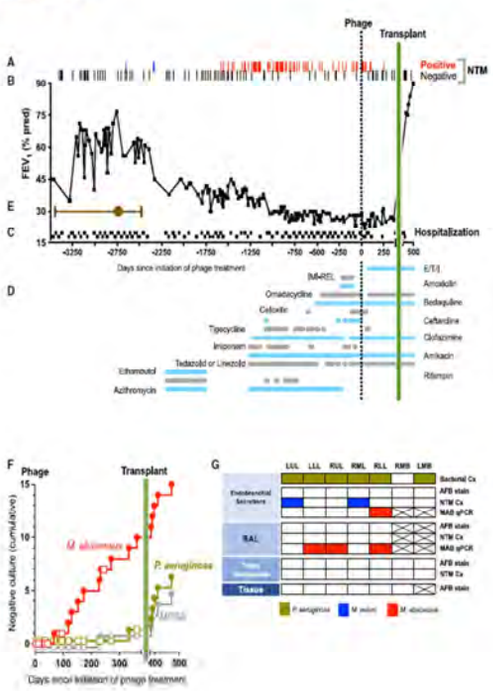
Cell

Host and pathogen response to bacteriophage engineered against *Mycobacterium abscessus* lung infection

Jerry A. Nick,[1,2,8] Rebekah M. Dedrick,[1] Alice L. Gray,[1] Ester K. Vladar,[1] Bailey E. Smith,[1] Krista G. Freeman,[1] Kenneth C. Malcolm,[1] L. Elaine Epperson,[1] Nabeeh A. Hasan,[1] Jo Hendrix,[1,3] Kimberly Callahan,[1] Kendra Wallace,[1] Brian Vestal,[1] Emily Wheeler,[1] Noel M. Rysavy,[1] Katie Poch,[1] Silvia Caceres,[1] Valerie K. Lovell,[1] Katherine B. Hisert,[1,3] Vinicius Calado de Moura,[1] Delphi Chatterjee,[4] Prithviraj De,[4] Natalia Weakly,[1] Stacey L. Martiniano,[1] David A. Lynch,[5] Charles L. Daley,[1,3] Michael Strong,[1] Fan Jia,[6] Graham F. Hatfull,[6,7] and Rebecca M. Davidson[6]
[1]Department of Medicine, National Jewish Health, Denver, CO 80206, USA
[2]Department of Medicine, University of Colorado School of Medicine, Aurora, CO 80045, USA
[3]Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA 15260, USA
[4]Center for Genes, Environment, and Health, National Jewish Health, Denver, CO 80206, USA
[5]Computational Bioscience Program, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA
[6]Mycobacteria Research Laboratories, Department of Microbiology, Immunology and Pathology, Colorado State University, 1682 Campus Delivery, Fort Collins, CO 80523, USA
[7]Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO 80045, USA
[8]Department of Radiology, National Jewish Health, Denver, CO 80206, USA
[9]Lead contact
*Correspondence: (J.A.N.), (G.F.H.)

SUMMARY

Two mycobacteriophages were administered intravenously to a male with treatment-refractory *Mycobacterium abscessus* pulmonary infection and severe cystic fibrosis lung disease. The phages were engineered to enhance their capacity to lyse *M. abscessus* and were selected specifically as the most effective against the subject's bacterial isolate. In the setting of compassionate use, the evidence of phage-induced lysis was observed using molecular and metabolic assays combined with clinical assessments. *M. abscessus* isolates pre and post-phage treatment demonstrated genetic stability, with a general decline in diversity and no increased resistance to phage or antibiotics. The anti-phage neutralizing antibody titers to one phage increased with time but did not prevent clinical improvement throughout the course of treatment. The subject received lung transplantation on day 379, and systematic culturing of the explanted lung did not detect *M. abscessus*. This study describes the course and associated markers of a successful phage treatment of *M. abscessus* in advanced lung disease.



- A cystic fibrosis patient
- 2 engineered phages cocktail
- General decline in bacterial diversity
- No increase in bacterial resistance to phages
- The patient got a lung transplantation at day 379
- No detected *M. abscessus* from explanted lung

6. Clinical Phage Therapy Cases in Journal Articles

(5) 2023 *M. abscessus*

Clinical Infectious Diseases
MAJOR ARTICLE

IDSA hivma OXFORD

Phage Therapy of *Mycobacterium* Infections: Compassionate Use of Phages in 20 Patients With Drug-Resistant Mycobacterial Disease

Rebekah M. Dedrick,[1] Bailey E. Smith,[1] Madison Cristinziano,[1] Krista G. Freeman,[1] Deborah Jacobs-Sera,[1] Yvonne Belessis,[2,3] A. Whitney Brown,[4] Keira A. Cohen,[5] Rebecca M. Davidson,[6] David van Duin,[7] Andrew Gainey,[8] Cristina Berastegui Garcia,[9] C. R. Robert George,[10] Gladys Haidar,[11] Winnie Ip,[12] Jonathan Iredell,[13] Ramneh Khatami,[14,15] Jessica S. Little,[16] Kirsi Malmivaara,[17] Brendan J. McMullan,[18] David E. Michalik,[19] Andrea Moccaldi,[20] Jerry A. Nick,[21] Maria C. Tapaycshi Ortiz,[22] Hari M. Polenakovik,[23] Paul D. Robinson,[24] Mikael Skurnik,[25,26] Daniel A. Solomon,[16] James Southall,[17] Helen Spencer,[27] Peter Wark,[27] Austea Wurth,[12] Robert T. Schooley,[28] Constance A. Benson,[28,a] and Graham F. Hatfull[1,a]

Background. Nontuberculous *Mycobacterium* infections, particularly *Mycobacterium abscessus*, are increasingly common among patients with cystic fibrosis and chronic bronchiectatic lung diseases. Treatment is challenging due to intrinsic antibiotic resistance. Bacteriophage therapy represents a potentially novel approach. Relatively few active lytic phages are available and there is great variation in phage susceptibilities among *M. abscessus* isolates, requiring personalized phage identification.

Methods. *Mycobacterium* isolates from 200 culture-positive patients with symptomatic disease were screened for phage susceptibilities. One or more lytic phages were identified for 55 isolates. Phages were administered intravenously, by aerosolization, or both to 20 patients on a compassionate use basis and patients were monitored for adverse reactions, clinical and microbiologic responses, the emergence of phage resistance, and phage neutralization in serum, sputum, or bronchoalveolar lavage fluid.

Results. No adverse reactions attributed to therapy were seen in any patient regardless of the pathogen, phages administered, or the route of delivery. Favorable clinical or microbiological responses were observed in 11 patients. Neutralizing antibodies were identified in serum after initiation of phage delivery intravenously in 8 patients, potentially contributing to lack of treatment response in 4 cases, but were not consistently associated with unfavorable responses in others. Eleven patients were treated with only a single phage, and no phage resistance was observed in any of these.

Conclusions. Phage treatment of *Mycobacterium* infections is challenging due to the limited repertoire of therapeutically useful phages, but favorable clinical outcomes in patients lacking any other treatment options support continued development of adjunctive phage therapy for some mycobacterial infections.

Keywords. phage therapy; nontuberculous mycobacteria; mycobacteriophage.

Table 2. Therapeutic Phages and Phage Sensitivities of Posttreatment *Mycobacterium* Isolates

Phages[a]	No. of Patients Treated	Phage Susceptibility of Phage Treatment Isolates[b,c]
Muddy	8	S – Patients 2, 5, 8, 11 (smooth and rough[d]), 13, 19 NA – Patient 16 NT – Patient 17
BPsΔ33HTH_HRM[ID93]	3	Only non-susceptible smooth strain recovered post treatment – Patient 7[d] NT – Patients 4, 6
Muddy, BPsΔ33HTH_HRM[ID93]	1	NA – Patient 9
Muddy, BPsΔ33HTH_HRM10, ZoeΔ45	2	S (BPsΔ33HTH_HRM10 and Muddy) – Patients 1, 12; PR (ZoeΔ45) – Patients 1, 12
BPsΔ33HTH_HRM[ID93], Itos	1	NT – Patient 10
BPsΔ33HTH_HRM10, Itos	2	S – Patient 19 NT – Patient 3
BPsΔ33HTH_HRM10, D29_HRM[ID90]	1	S – Patient 15
BPsΔ33HTH_HRM[ID93], D29_HRM[ID90]	1	NT – Patient 14
Muddy, D29, FionnbharthΔ43Δ45, Fred313cpmΔ33	2	NT – Patient 20

Abbreviations: NA, not applicable (no posttherapy isolates were grown); NT, not tested; PR, partially resistant; S, sensitive.

[a]Phages were used therapeutically either singly, or in the combinations shown.

[b]Patient numbers are as shown in Tables 1 and 3.

[c]Strains from patients were tested for changes in phage sensitivity. Strains were initially sensitive to the phages used therapeutically. For each patient, strains isolated after the start of phage treatment are shown as being phage sensitive, partially resistant, or not tested. Multiple samples from the same patients were tested similarly.

[d]Indicates patient with a mixed smooth and rough colony morphology *Mycobacterium abscessus* infection. For patient 11, both smooth and rough morphotypes were recovered during treatment and both morphotypes remained fully susceptible to Muddy, although the smooth strain is not killed by Muddy. For patient 7, only smooth isolates were found intratreatment, and only smooth isolates were tested for phage susceptibility.

- 20 patients infected with *M. abscessus*
- 1 or more phages cocktail
- Administered IV and/or IN
- Favorable clinical or microbiological responses from 11 patients
- Neutralizing antibody appeared from 8 patients
- No phage resistance developed from 11 patients with a single phage treatment

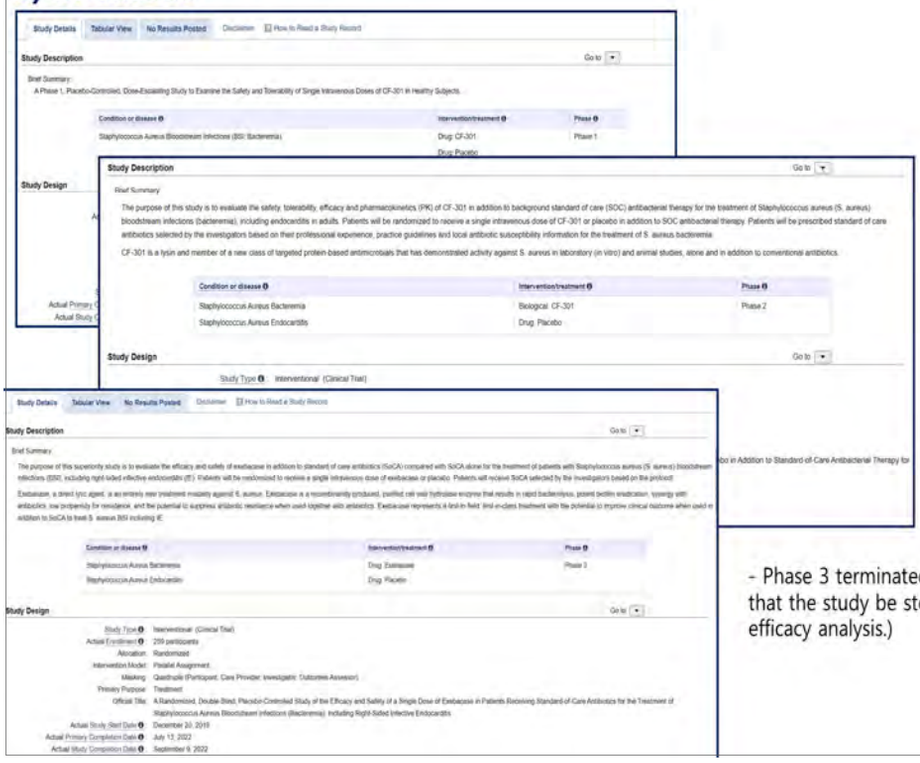
7. Company sponsored PT clinical trials

Modality	Company	Category	Indication	Target Bacteria	Clinical Stage
Endolysin	Contrafect	Infectious diseases	Systemic Infection	S. aureus	Phase 3
	Gangagen	Infectious diseases	Chronic kidney disease with nasal carriers	S. aureus	Phase 2
	Micreos	Infectious diseases	Atopic dermatitis	S. aureus	Phase 1/2a
	Intron Bio	Infectious diseases	Systemic Infection	S. aureus	Phase 2
Phage Therapy	Adaptive Phage Therapeutics	Infectious diseases	Respiratory Infection	P. aeruginosa	Phase 1/2
	Locus Biosciences	Infectious diseases	Urinary tract Infection	E. coli	Phase 2/3
	Phagelux	Infectious diseases	Wound Infection	S. aureus, P. aeruginosa or K. pneumoniae	Phase 1
	Armata	Infectious diseases	Skin wound	S. aureus	Phase 1
	Armata	Infectious diseases	Cystic fibrosis	P. aeruginosa	Phase 1/2
	Intralytix	Infectious diseases	Crohn`s disease	AIEC	Phase 1/2
	BiomX	Infectious diseases	Cystic fibrosis	P. aeruginosa	Phase 1/2
	Yale Univ.	Infectious diseases	Cystic fibrosis	P. aeruginosa	Phase 1/2
	Certre Hospitalier.	Infectious diseases	Diabetic foot	S. aureus	Phase 1/2

(www.clinicaltrials.gov)

8. Endolysin Clinical Trials
1) *S. aureus*

ContraFect
MOLECULAR TREATMENTS FOR INFECTIOUS DISEASE



- Phase 3 terminated (the independent DSMB recommended that the study be stopped for futility following interim efficacy analysis.)

8. Endolysin Clinical Trials
2) *S. aureus*

iNtRON BIOTECHNOLOGY

roivant

- The original developer (Intron Bio) licensed out to Roivant during a phase 2 investigation
- Roivant cancelled its phase 2 trial and returned the right to Intron Bio.

Take Home Points

1. Bacteriopahges are good candidates for treating MDR pathogens. Their efficacy was proven *in vitro* and *in vivo*.
2. In the future, fixed cocktails can be used first line, followed by personalized phages.
3. For personalized therapy, phages need to be produced in every hospital participating in PT.
4. Generally no adverse effect was reported from clinical phage therapies.
5. Immune clearance of phages was observed in some immunocompetent patients leading to decreased efficacy, but not all.
6. Endolysins are good candidates for treating MDR pathogens. Their efficacy was proven *in vitro* and *in vivo*.
7. Proof of concept clinical trials of endolysins are expected in a near future.

Thank you !!

2. NIH-Supported Clinical Trial of Phage Therapy for Cystic Fibrosis Begins

Dr. Dennis Dixon (NIAID, USA)

Dennis M. Dixon

Chief, Bacteriology and Mycology

NIH/NIAID

- **EDUCATION:**

BS, Biology	University of Richmond, Richmond, VA
PhD, Microbiology	Medical College of Virginia, Richmond, VA

- **PROFESSIONAL EXPERIENCE:**

Associate Professor of Biology	Loyola of Baltimore, MD
Associate Professor of Dermatology (Adjunct)	University of Maryland School of Medicine, Baltimore, MD
Visiting Scentist (Sabbatical)	Hoffmann LaRoche, Basel, Switzerland
Director, Mycology Clinical Reference Laboratory	New York State Department of Health, Albany, NY
Assistant Professor of Pathology (Adjunct)	Albany Medical College, Albany, NY

- **SUMMARY**

Topic: **NIH/NIAID, Antibacterial Resistance and Our Bacteriophage Trial in Cystic Fibrosis Paients.**

Abstract

The NIH is the largest public funder of biomedical research in the world, and the NIAID is the lead institute on antibacterial resistance (AR). Clearly AR is a major public health problem. The GRAM report, Lancet (2022) 399:629-655, documented that a sort list of of resistant bacterial pathogens were carefully estimated to cause more deaths globally than AIDS and malaria combined. This presentation will summarize an overview of NIAID efforts to address the global threat of antimicrobial resistance, including research on alternative treatments with a focus on the NIAID Antibacterial Resistance Leadership Group (ARLG) trial on a prospective, randomized clinical trial to study safety

and activity of a bacteriophage approach to addressing Pseudomonas infection in cystic fibrosis (CF) patients. It is hoped that this rigorous, prospective trial will provide valuable, foundational information on safety and activity of intravenously administered bacteriophage on Pseudomonas colony counts on stable CF patients colonized with Pseudomonas and titres of bacteriophage after administration. I addition, a summary will be given of the recent guidance type document from the ARLG and the NIAID on summary of bacteriophage therapy and possible adjunctive therapeutic indications.

NIAID, Antibacterial Resistance, and Antibacterial Resistance Leadership Group Bacteriophage Trial

Dennis M. Dixon, PhD
Chief, Bacteriology and Mycology Branch
Division of Microbiology and Infectious Diseases
NIAID, NIH

22 February 2023
Korean Institute of Infectious Diseases Meeting
Jeju Island, South Korea

National Institute of Allergy and Infectious Diseases

NIH and NIAID

NIH. National Institutes of Health.

- Largest public funder of biomedical research worldwide.

Former Director: Francis Collins, M.D., Ph.D.
Acting Director: Lawrence Tabak, D.D.S., Ph.D.

NIAID. National Institute of Allergy and Infectious Diseases.

- Lead institute on antimicrobial and antibacterial resistance.

Former Director: Anthony Fauci, M.D.
Acting Director: Hugh Auchincloss, M.D.

International and National Strategies: NIH role

Transatlantic Taskforce on Antimicrobial Resistance — **TATFAR**

EXPERTS UNITE ACROSS BORDERS TO IMPROVE ANTIBIOTIC USE IN HUMANS AND ANIMALS, PREVENT INFECTIONS AND THEIR SPREAD, AND STRENGTHEN THE DRUG PIPELINE.

TATFAR was created in 2009 to address the urgent threat of antimicrobial resistance (AMR). Collaboration across government agencies from Canada, EU, Norway, and U.S. enhances synergy and communication, leading to strengthened domestic and global efforts.

2021-2026

Key Focus Areas

- Improve antibiotic use in humans and animals
- Prevent infections and their spread
- Strengthen the drug pipeline

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

2020-2025

October 2020

- **Diagnostics:** advance development and use of rapid and innovative tests
- **Countermeasures:** accelerate basic and applied research and development for new antibiotics, other therapeutics and vaccines

NIAID Bacteriophage Activities

NCATS-NIAID Joint Workshop on Bacteriophage Therapy

October 25, 2022
9:00 AM-5:00 PM
Viewing in Eastern Time

6701 Rockledge Drive, Bethesda, MD 20817, Rockledge II Room 160
6705 Rockledge Drive
Bethesda, 20817

FDA

WORKSHOP

Science and Regulation of Bacteriophage Therapy Workshop

AUGUST 30, 2021 - SEPTEMBER 1, 2021

https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/science-and-regulation-bacteriophage-therapy-workshop-08302021

- DMID Director visited the Phage Therapy Unit at Polish Academy of Sciences
- Phage therapy workshops hosted by NIAID-NCATS and NIAID-FDA
- Phage PCS Services:
  - *in vitro* susceptibility testing
  - *in vivo* efficacy in the mouse thigh, lung, peritonitis and bacteremia models
  - *in vivo* 'PK' with phage quantitation by qPCR or plaque assay

Targeted Funding: Special Needs, RFA, RFP, Etc.

FY	Solicitation	Title of Initiatives	# Awarded
2015	RFA-AI-14-026	Development of Novel Therapeutics for Select Pathogens (R21/R33)	21
2016	RFA-AI-14-066	Non-Traditional Therapeutics That Limit Antibacterial Resistance (R21/R33)	24
2016	RFA-AI-15-024	Partnerships for the Development of Host-Targeted Therapeutics to Limit Antimicrobial Resistance (R01)	5
2018	RFA-AI-17-017	Partnerships for the Development of Vaccines and Immunophrophylactics Targeting Multiple Antimicrobial-Resistant Bacteria (R01)	3
2019	RFA-AI-17-026	Partnerships for Countermeasures Against Select Pathogens (R01)	15
2019	RFA-AI--19-065	Understanding Phage Biology to Support the Development of Bacteriophage Therapy (R21)	14
2021	RFA-AI-20-001	Combating Antibiotic-Resistant Bacteria (CARB) Interdisciplinary Combating Antibiotic-Resistant Bacteria (CARB) Interdisciplinary Research Units: U19 Clinical Trial Not Allowed)	3
2021	RFA-AI-20-028	Partnerships for Countermeasures against Select Pathogens (R01 Clinical Trials Not Allowed)	5
2021	SBIR Contract	Improving Technologies to Make Large-scale High Titer Phage Preps	3
2021	BAA 2020	Development of Medical Countermeasures for Biothreat Agents, Antimicrobial-Resistant Infections, and Emerging Infectious Diseases	TBD

NIAID Antibacterial Resistance Leadership Group (ARLG)

Launched in June 2013 and renewed in 2019 to **develop**, **prioritize**, and **implement** a clinical research agenda to impact antibacterial resistance

METRICS FROM ORIGINAL ARLG FUNDING PERIOD

Clin Infect Dis, Volume 73, Issue 4, 15 August 2021

- To date, the ARLG has
  - reviewed **>175** study proposals
  - initiated **>60** studies
  - included data from **>27,000** subjects
  - published **>220** manuscripts
  - obtained **2** FDA approvals

ARLG Antibacterial Resistance Leadership Group https://arlg.org/

ARLG Phage Trial

NEWS RELEASES

NIH National Institutes of Health
Turning Discovery Into Health

NIH-supported clinical trial of phage therapy for cystic fibrosis begins

Antimicrobial Agents and Chemotherapy

MINIREVIEW

March 2022 Volume 66 Issue 3 e02071-21

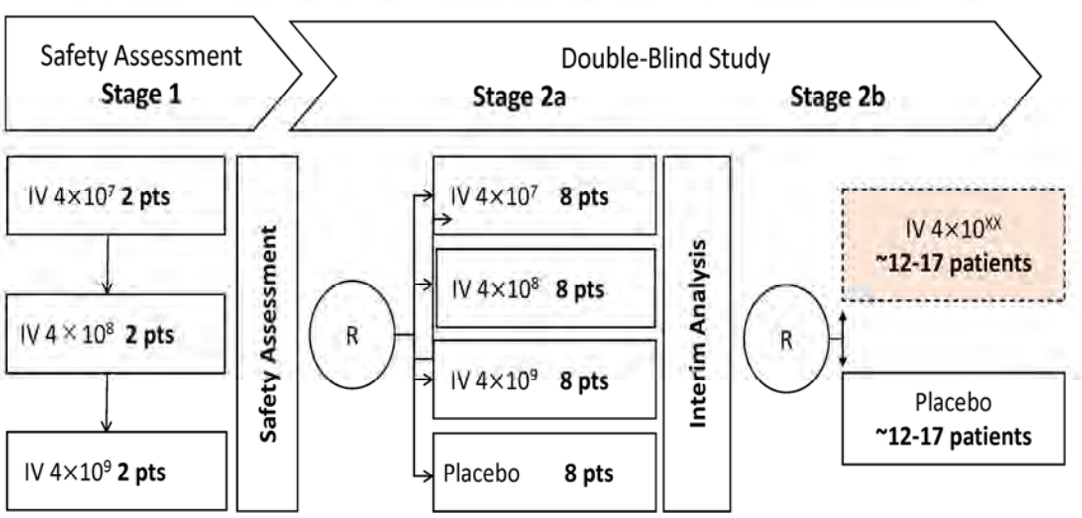
Considerations for the Use of Phage Therapy in Clinical Practice

Suh, G. A. *et al.*
for the Antibacterial Resistance Leadership Group

Key Points

- Phase 1b/2 trial of IV of phage cocktail in CF patients colonized with *P. aeruginosa*
  - 72 patients in 14 centers
  - Enrollment started in September 2022
- Objectives:
  - Determine dose-effects for PK/PD
  - Evaluate safety and microbiological activity of bacteriophage therapy
- A comprehensive review to inform clinicians considering experimental phage therapy

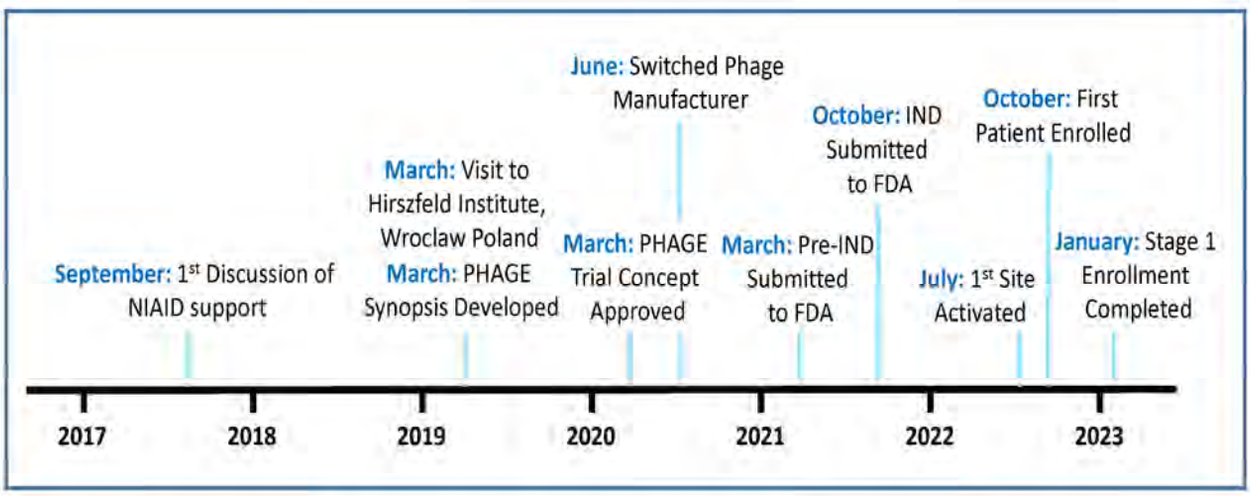
PHAGE - Trial Design



Optimal sample size and phage dose for Stage 2b will be determined during the interim analysis. Bacteriophage mixture consists of a 4-phage mixture at a ratio of 1:1:1:1.

ARLG

PHAGE Clinical Trial Timeline



Anticipate enrollment completion by January 2024.

NIAID ARLG Phage Trial: Challenges

- Separating anecdotes from data
- Selecting a target population.
  - Chip Schooley MD – UCSD; Cystic Fibrosis (CF) patients
- Partnerships: 5 trips to the church
- Pioneering a regulatory pathway
- Publishing a "phage guidance document" (ARLG, NIAID, FDA)
- Selecting a candidate phage or phage cocktail.
  - Selecting optimal phage mixture, stability and susceptibility
- Identifying eligible stable CF patients colonized with *Pseudomonas*
- Advances in CF treatment
  - Trikafta®, triple combination of two correctors, Elexacaftor (VX-445) and Tezacaftor, together with the potentiator, Ivacaftor, for patients bearing the F508del mutation in at least on one allele

Phage Taskforce Recommendations for the Clinical Use of Phage

Parameters
- Task force from ARLG, NIAID, FDA, other experts
- Literature review of nearly15,000 English abstracts from 2000 -2020 screened with ~ 1,000 selected
- "Clinical Practice Guidelines" approach

Three Themes
- Potential clinical situations
- Laboratory testing
- PK considerations

Key Clinical Indications
- Antibiotic-refractory respiratory infections
- Device/biofilm associated infections such as osteoarticular, endovascular, UTI, GI

Bottom Line: ***"There is a near total lack of randomized controlled trials of phage therapy."***

The Power of Networking

- Domestic Examples
  - Clinical Trial Networks (ARLG)
  - US Interagency Task Force on AR
- International Examples
  - TATFAR (Trans Atlantic Task Force on AR) currently US + European Union + Norway + Canada
- TPTFAR – "Trans-Pacific Task Force" on AR?
  - Tokyo AMR/One Health Meetings March and February 2021 and 2022
  - US-Japan Emerging Infections Meeting Seoul, February 2016
  - Communication, communication, communication

Thank you

… For your interest

Part 3. Research of Vaccine adjuvants

Chair:
Baik-lin Seong, M.D., PhD.

1. Flagellin as a potent immune modulator for the elderly
Dr. Kyung-a Cho (Medispan Inc., Korea)

2. Vaccine adjuvants research
Dr. Kentner Leroy Singleton (NIAID, USA)

3. The future of pandemic preparedness: Building collaborations and EV-D68 as a test case for NIAID/VRC's PREMISE program
Dr. Alicen Spaulding (NIAID, USA)

Part 3. Research of Vaccine adjuvants

Moderator

Baik-Lin Seong

Professor

Distinguished Professor & Director General, Vaccine Innovative Technology ALliance (VITAL)-Korea

Yonsei University College of Medicine

- **EDUCATION:**

1988	Massachusetts Institute of Technology, PhD
1979	Korea Advanced Institute of Science and Technology, MS
1977	Seoul National University, BS

- **PROFESSIONAL EXPERIENCE:**

2022 ~ Present	Chair, Division of Biotechnology, Science & Technology Advisory Board, MoFA, Korean Government
2020 ~ Present	Distinguished Professor, Yonsei University College of Medicine
2020 ~ Present	Director General, Vaccine Innovative Technology ALliance (VITAL)-Korea
2020 ~ 2022	Chair, COVID-19 Vaccine Pan-Government Strategic Plan, Korean Government
2020 ~ 2021	Member, Presidential Advisory Council on Science & Technology, Korean Government
2000 ~ 2009	CEO, Protheon
1998 ~ 2020	Professor, Department of Biotechnology, Yonsei University
1993 ~ 1998	Director, Institute of Biological Sciences, Hanhyo Institute of Technology
1992 ~ 1993	Scientist, Aviron, USA
1988 ~ 1992	Postdoctoral Scientist, University of Oxford, UK

Part 3

Research of Vaccine adjuvants

1. Flagellin as a potent immune modulator for the elderly

Dr. Kyung-a Cho (Medispan Inc., Korea)

Kyung-A Cho

Professor, CEO

Department of Biochemistry, Chonnam National University Medical School

MediSpan, Inc

- **EDUCATION:**

1999 ~ 2002	PhD, Seoul National University College of Medicine
1997 ~ 1999	M.S, Hallym University College of Medicine
1993 ~ 1997	B.A, Kangwon National University

- **PROFESSIONAL EXPERIENCE:**

2020 ~ Present	CEO, MediSpan. Co., Ltd
2015 ~ Present	A board member of the Korea Support Committee for International Vaccine Institute (IVI)
2020 ~ Present	An Executive Committee member of the Korean Society for Gerontology
2020 ~ 2022	Vice Dean, Chonnam National University Medical School
2015 ~ Present	Professor, Department of Biochemistry, Chonnam National University Medical School
2010 ~ 2015	Associate Professor, Department of Biochemistry, Chonnam National University Medical School
2010 ~ 2015	Assistant Professor, Department of Biochemistry, Chonnam National University Medical School
2002 ~ 2006	Post Doc, Department of Biochemistry and Molecular Biology, Seoul National University College of Medicine

• SUMMARY

Topic: Flagellin as a potent immune modulator for the elderly

Abstract

Immunological alteration with age results in increased susceptibility to infectious diseases and poor vaccination outcomes. In a previous study, we proved that the specific form of Toll-like receptors 5 (TLR5) could be a good target for vaccine adjuvant for the elderly (Lim JS et al., 2015. Aging Cell). Furthermore, we showed mucosal TLR5 stimulation protects from aging-associated diseases (such as lung fibrosis) and aging-associated comorbidities, including hair loss, ocular lens opacity, decreased bone mineral density, reduced bone marrow-derived stem cell activity, immunological functions, and compromised cognitive capacity (Lim JS et al., 2023. processing in Nat. Comn). Bacterial flagellin, known as a ligand for TLR5, consists of four domains: D0 – D3. Among them, the D1 domain directly binds to TLR5, and the D2 and D3 domains are hypervariable regions exposed to the outside and induce strong immunogenicity. Previously Salmonella flagellin has been developed as an influenza vaccine adjuvant for the elderly. However, high antibody production and CRP generation by D2-D3 domains of flagellin led to a stop in the clinical trials. To improve these limitations, we have developed modified flagellin (MSP-102) that minimizes the immunogenicity of the existing flagellin and improves stability. At this conference, we want to introduce MSP-102 as a novel therapeutic target for vaccine adjuvants for the elderly.

Topic: Development of the novel Tuberculosis vaccine applied to various platforms in Korea

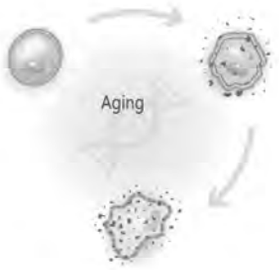
Abstract

Tuberculosis (TB) is the second leading infectious cause of mortality worldwide, with about two million deaths yearly. Globally in 2020, an estimated 5.8 million incident cases were caused by M. tuberculosis. Moreover, there are an estimated 1.3 million deaths from TB. South Korea ranked the highest TB incidence among the Organization for Economic Cooperation and Development (OECD) members. The only licensed vaccine, Mycobacterium bovis Bacillus Calmette Guerin (BCG), is effective in infants and adolescents. Unfortunately, the varying immune efficacy and short duration cause limited protection effects, so the BCG vaccine does not protect all generation groups from tuberculosis. Although significant progress in the search for a more effective TB vaccine has been demonstrated over the last two decades, there is still no replacement for the licensed BCG vaccine. Since 2018, the Korean government has implemented the "Midterm strategies to strengthen TB prevention and management" based on the 2nd National Strategic Plan for Tuberculosis Control (2018-2022). The program includes a strategy to support the development of a new tuberculosis vaccine. In this session, we would like to introduce the developing status of the new tuberculosis vaccine using various platforms and new formulation, in Korea.

Flagellin, as a potent immune modulator for the elderly
Medicine for Healthy Life Span
MediSpan

Contents
❖ TLR5 controls healthspans and longevity by overcoming immunosenescence.
❖ MSP-102 is a potent and safely engineered flagellin.

Aging causes geriatric diseases



Increased chronic inflammation

Aging-related various diseases

Cancer, Alzheimer's, Parkinson's, non-alcoholic steatohepatitis, osteoarthritis, osteoporosis, pulmonary fibrosis, sarcopenia, rheumatoid arthritis, metabolic diseases, etc.

Immunosenescence

- ✓ High susceptibility to infections
- ✓ Decreased vaccine efficacy
- ✓ Failure of immunotherapy for cancer, etc.

Causes of increased deaths among the elderly in the pandemic

Development of immune enhancement for the elderly

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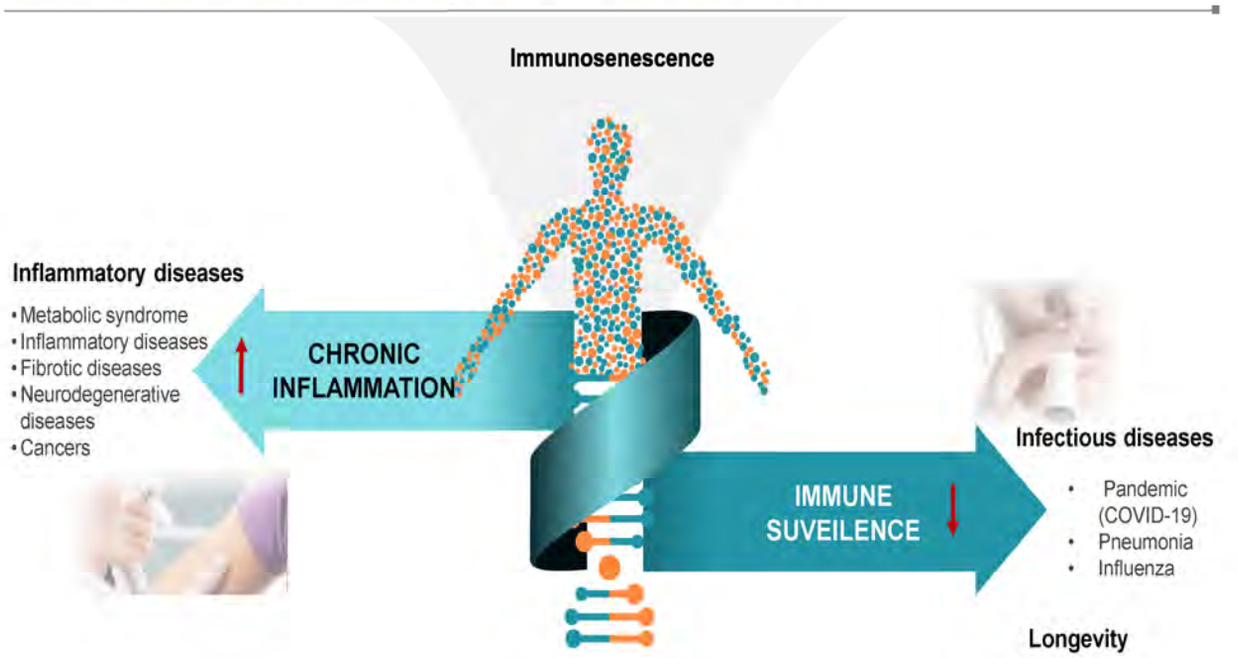
Immunosenescence & age-related diseases



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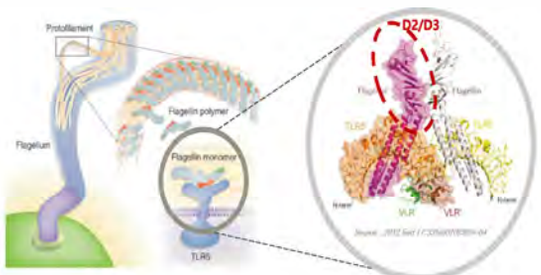
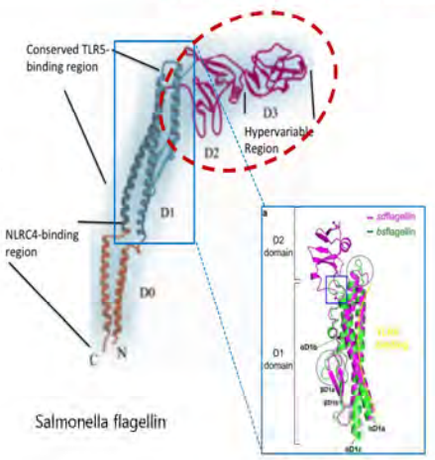
Flagellin



High immunogenic regions



Salmonella flagellin

Conserved structure for binding with TLR5

D1 domains
- TLR5 binding site
- Conserved structure in various bacterial strains

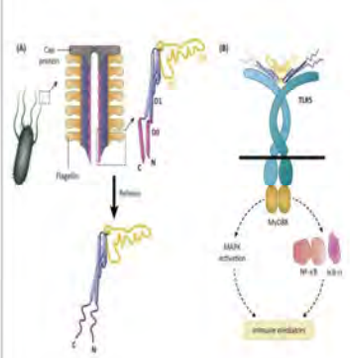
D2 and D3 domains
- No contribution to filament formation and TLR5 stimulation
- Hypervariable region
- Cause the undesirable toxicity of flagellin-based therapeutics

Target: TLR5

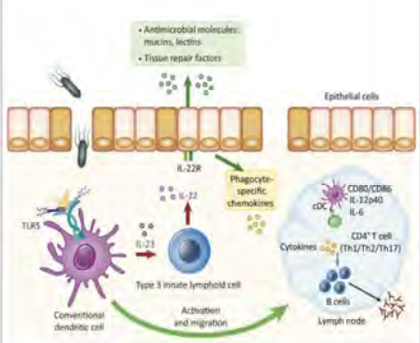
TLR5

- Innate immune receptor of **bacterial flagellin**
- Mediating various immune responses via MAPK and NF-kB signaling
- Major target of **vaccine adjuvant developments**
- Major target of diseases: cancer, inflammatory bowel diseases (IBD), acute radiation syndrome (ARS), metabolic syndrome

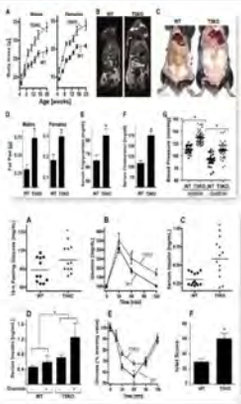
TLR5 recognizes bacterial flagellin



TLR5-dependent antimicrobial functions & Tissue regeneration via IL-22



TLR5 protects metabolic syndromes via regulating dysbiosis



Influenza vaccine with flagellin for the elderly

TLRs in the elderly

- Reduced surface expression of TLRs 1 and 4 in monocytes and DC of elderly human donors
  [*J. Immunol.* 2007b;178:970–975; *J. Immunol.* 2010;184:2518–2527]
- Reduced levels of certain TLRs and diminished TLR signaling likely contribute to impaired immune responses and the increases in morbidity and mortality noted in elderly populations
  [*Ageing Res. Rev.* 2011;10:346–353]
- TLR5 expression and mediated signaling are well maintained in the elderly
  [*Mech. Ageing Dev.* 2006: *Vaccine.* 2008: *Vaccine.* 2009;28:4103–4112; *Vaccine.* 2011;29:4897–4902: *Aging Cell* 2012: *Aging Cell* 2015]

❖ To improve vaccination efficiency for the elderly, several influenza-flagellin fusion vaccine formulations in clinical trials

Table 4. PBAs with TLR5 adjuvant potential.

Specie	PBA	Innate Immune Response	Adaptive Immune Response
Salmonella strains	Flagellin	NF-kB and MAPKs activation. Induction of proinflammatory mediators resulting in the upregulated expression of cytokines, such as TNF-α, IL-6, IL-8, and proinflammatory free radical synthesizing enzymes, such as the inducible nitric oxide synthase	Efficient immune response in elderly subjects immunized with recombinant hemagglutinin influenza–flagellin fusion vaccine (VAX125)

✓ However, the high titer of antibodies produced by immunogenic D2-D3 regions of flagellin limits flagellin efficacy as a vaccine adjuvant.

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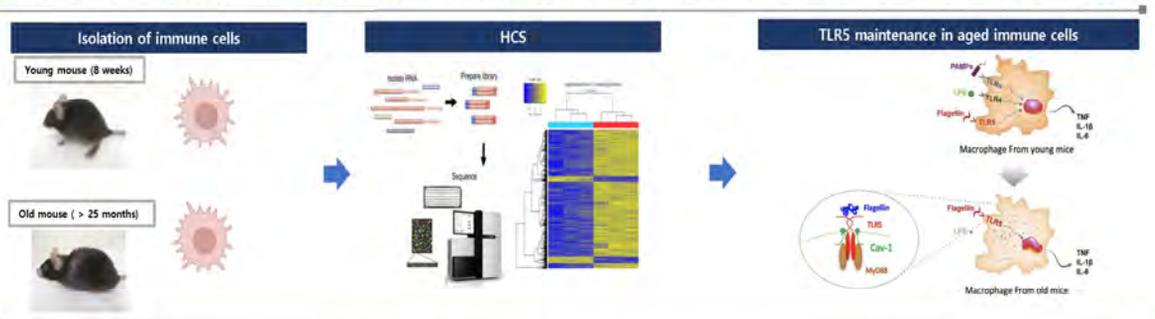
Flagellin conjugated pneumonia vaccine (MSP-101) for the elderly



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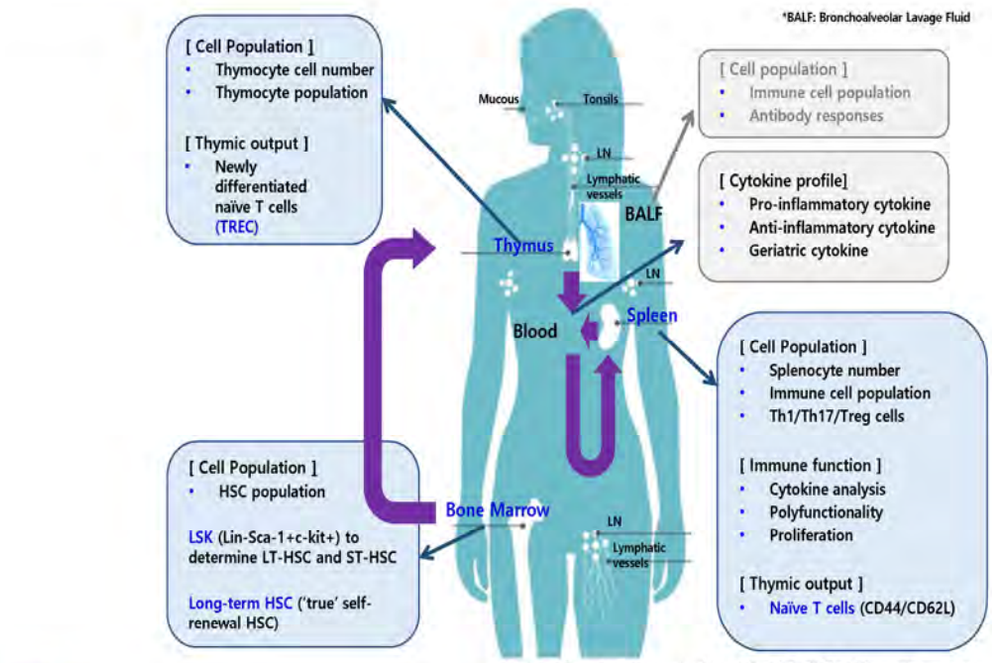
※ JS Lim et al., Aging Cell. 2015; JS Lim et al., Mol Cells. 2015

Screening strategy of immune systems in old animal



Modified from, http://www.nia.nih.gov/sites/default/files/9_immune_system.jpg

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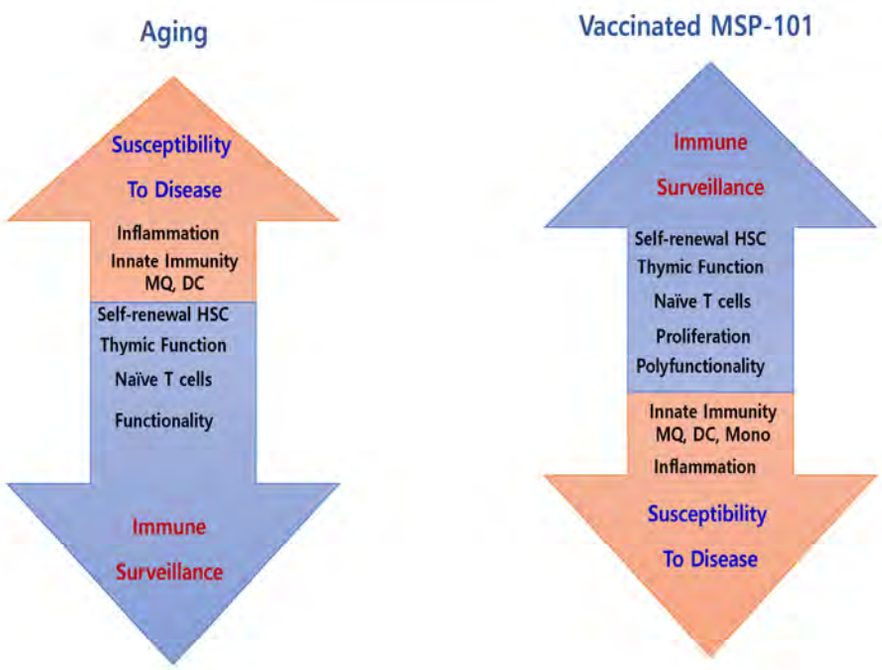
Summary of flagellin adjuvanted vaccine effects in old animals



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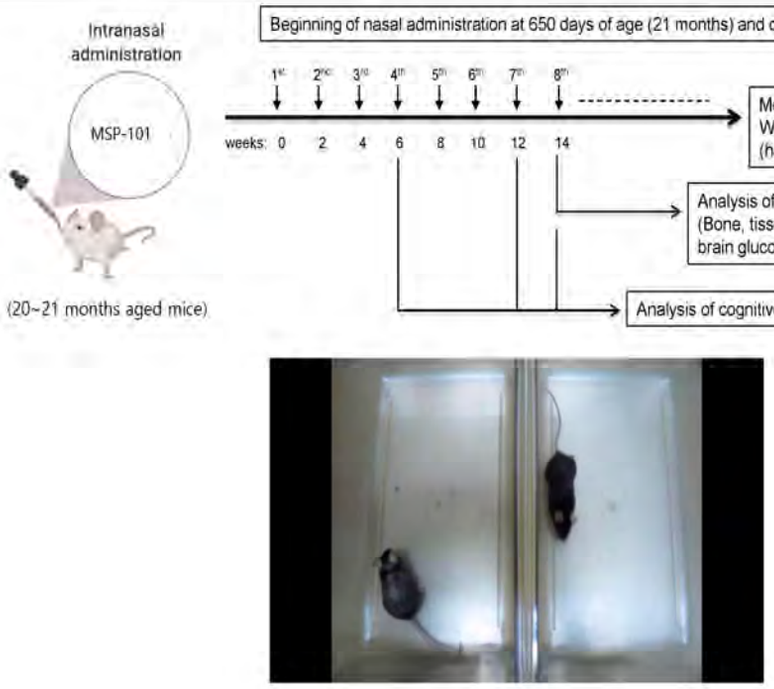
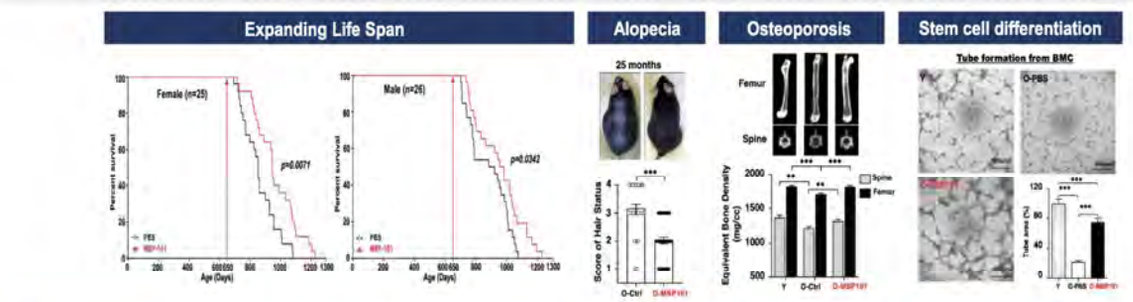
Flagellin leads to the longevity with beneficial health effects

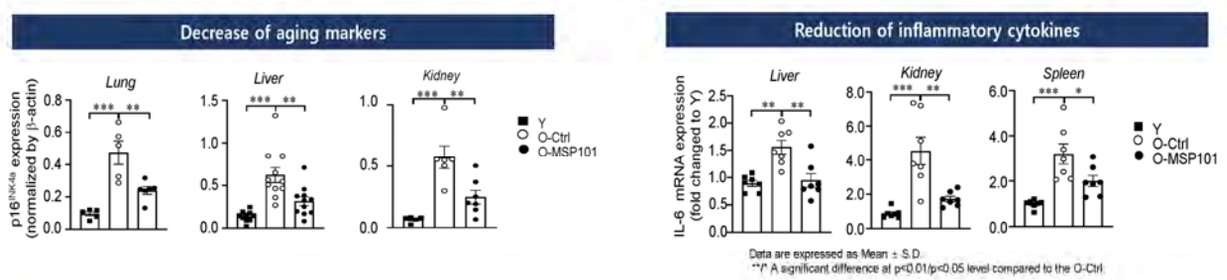


Flagellin leads to the longevity with beneficial health effects

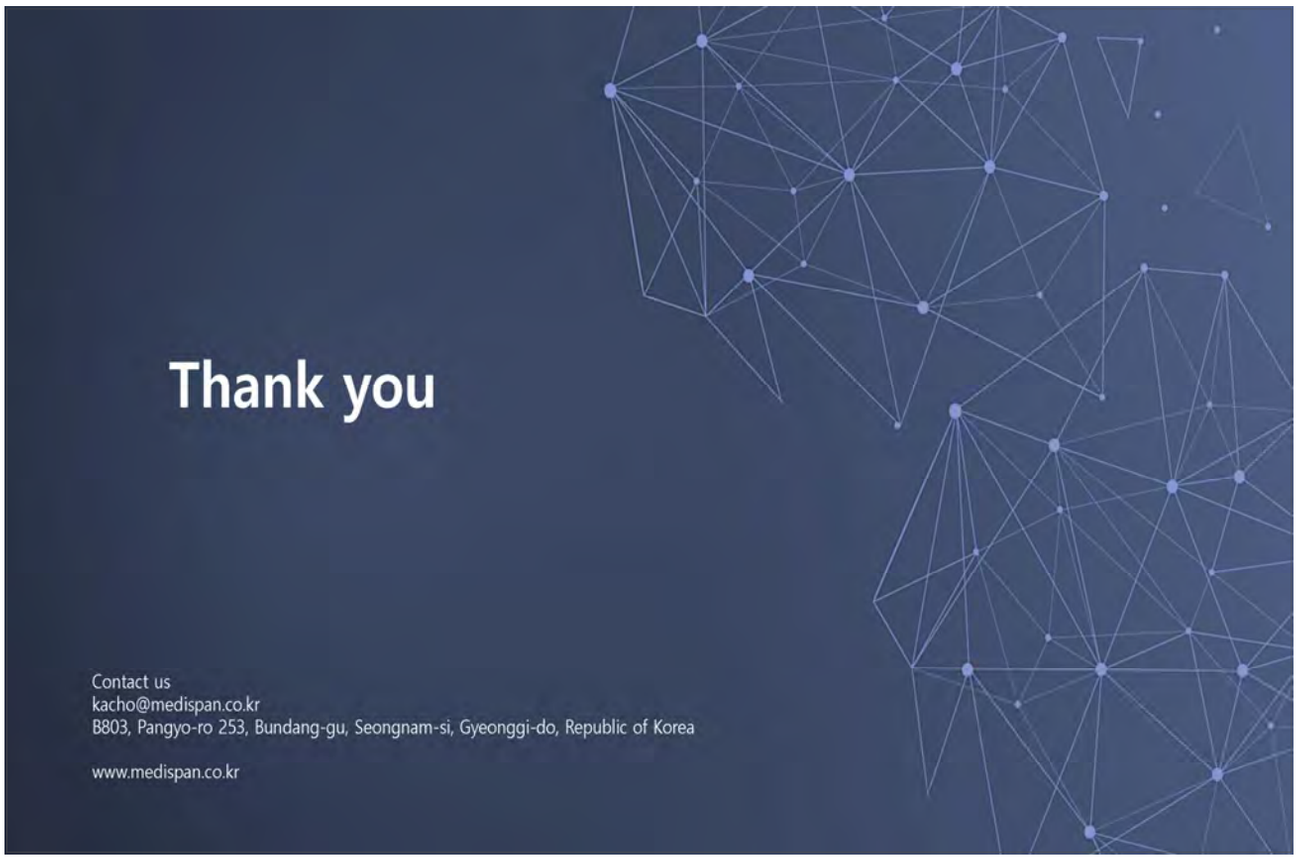
Longevity

- MSP-101 leads longevity with a broad ranges of beneficial health effects
- MSP-102 is an optimized drug of MSP-101





Data are expressed as Mean ± S.D.
"/" A significant difference at $p<0.01$/$p<0.05$ level compared to the O-Ctrl.


Thank you
Contact us
kacho@medispan.co.kr
B803, Pangyo-ro 253, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea
www.medispan.co.kr

2. Vaccine adjuvants research

Dr. Kentner Leroy Singleton (NIAID, USA)

Kentner L. Singleton

Program Officer, Basic Immunology Branch; Division of Allergy Immunology and Transplantation

National Institute of Allergy and Infectious Diseases (NIAID)

- **EDUCATION:**

University of Texas Southwestern Medical Center	Dallas, TX
	Ph.D., Immunology, 2010
University of Washington	Seattle, WA
	Bachelor of Science, Biochemistry, 1999

- **PROFESSIONAL EXPERIENCE:**

2014 ~ Present	Program Officer Basic Immunology Branch; Division of Allergy Immunology and Transplantation; National Institute of Allergy and Infectious Diseases (NIAID); National Institutes of Health (NIH); Bethesda, MD
2014 ~ 2014	Detail Extramural Program; Division of Skin and Rheumatic Diseases; National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); NIH; Bethesda, MD
2010 ~ 2014	Pharmacology Research Fellow Intramural Program; Molecular Immunology and Inflammation Branch; NIAMS; NIH; Bethesda, MD Mentor: John J. O'Shea, MD Research: Identification of genetic regions that regulate inflammation and mechanisms of action
2010 ~ 2014	Instructor (Immunology) The Catholic University of America; Washington D.C.

• PROFESSIONAL EXPERIENCE:

2003 ~ 2010	Graduate Student Department of Immunology; University of Texas Southwestern Medical Center; Dallas, TX Mentor: Christoph Wulfing, PhD Research: System-scale characterization of T cell signaling via quantitative live cell imaging
1999 ~ 2003	Research Technician Human Immunogenetics Program; Fred Hutchinson Cancer Research Center; Seattle, WA Mentor: John A. Hansen, MD Research: Identification of genotypes that predict clinically significant posttransplant complications and the development of immune tolerance
1997 ~ 1999	Undergraduate Research Department of Chemistry; University of Washington; Seattle, WA Mentor: Craig Beeson, PhD Research: Determination of the relative energetics of binding interactions between peptides and MHC Class II

• SUMMARY

Topic: NIAID Vaccine Adjuvant Program

Abstract

The National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), supports a comprehensive Vaccine Adjuvant Program to advance the discovery, development, and characterization of new vaccine adjuvants. These adjuvants may be used to improve the efficacy of current vaccines, design new or improved vaccines for existing and emerging infectious diseases, and develop vaccines to treat allergies, autoimmune diseases, substance use disorders, and cancer. The NIAID Adjuvant Program has supported the screening of over 2 million compounds and the development 〉40 adjuvants, which have been evaluated in more than 25 clinical trials. Vaccine adjuvants available for use by investigators may be found at the Vaccine Adjuvant Compendium (https://vac.niaid.nih.gov/). The compendium compiles metadata on novel adjuvant research and characteristic studies to help vaccine developers identify suitable adjuvants.

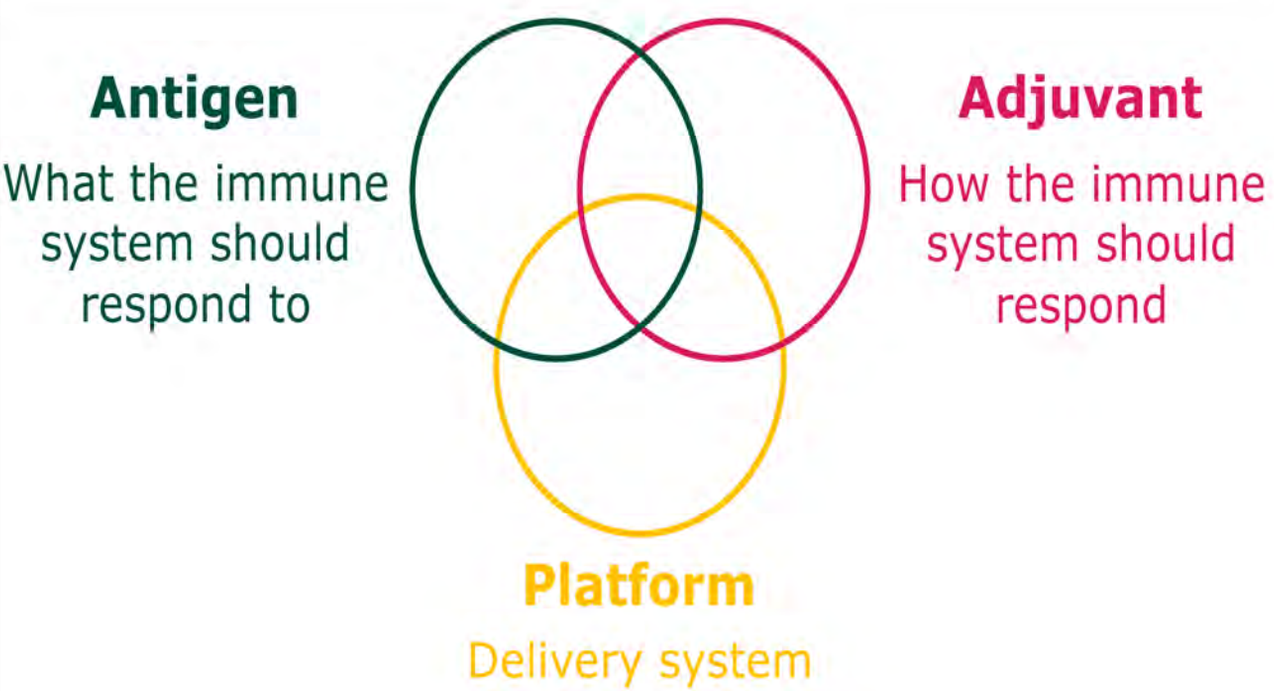
NIAID Vaccine Adjuvant Program

Kentner Singleton, Ph.D.
Program Officer
Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases

singletonkl@niaid.nih.gov

National Institute of Allergy and Infectious Diseases

Components of a Vaccine



Need for Vaccine Adjuvants

- Induce desired type of immune response
  - Th1, Th2, Th17
  - Humoral, cellular
- Optimize immune response to a vaccine
  - Onset, magnitude, breadth, duration, antigen sparing
  - Reduce reactogenicity
  - Target specific tissues / organs
- Improve efficacy in vulnerable populations
  - Elderly, newborns, immunocompromised patients
- Availability

Objectives of NIAID's Adjuvant Program

- Discovery
  - Pipeline of new immune stimulators
  - Exploration of combination adjuvants
- Basic research
  - Mechanisms of action, correlates of adjuvanticity
- Pre-clinical development
  - Bring novel adjuvants to the clinic
  - Head to head adjuvant comparison in pre-clinical models
- Expand access
  - Connect vaccine and adjuvant developers

Initiatives of NIAID's Adjuvant Program

- Discovery
  - Adjuvant Discovery Program (2004, 2009, 2014, 2019; 2024, annual SBIR)
- Basic research
  - Molecular Mechanisms of Combination Adjuvants (2016, 2021)
- Pre-clinical development
  - Adjuvant Development Program (2008, 2013, 2018, 2023; annual SBIR)
  - Advancing Vaccine Adjuvant Research for Tuberculosis (2022)
  - Adjuvant Comparison and Characterization (2022)
- Expand access
  - NIAID Strategic Plan for Research on Vaccine Adjuvants (2018)
  - Vaccine Adjuvant Compendium (https://vac.niaid.nih.gov/) (2021)

Adjuvant Discovery Program

Program Structure

High-throughput screening
↓
Mechanisms of action
↓
Structure-activity relationship
↓
In vivo testing, further down-selection

Screening

- *In vitro* (>$2x10^6$)
- *In silico* (>10^{24})

Targets/Receptors

- CLR (Dectin, Mincle)
- Cytokine receptors
- IRF (1, 3, 5, 7)
- Kinase inhibitors
- NF-kB modulator/inhibitors
- NOD-1
- RIG-I
- STING
- TLR (2, 4, 7, 8, 9)
- Unknown

Classes of Compounds

- Natural compounds
- Synthetic small molecules
- Proteins, peptides
- Aptamers

Adjuvant Development Program

- Pre-clinical development of vaccine adjuvants
  - Animal studies, formulation, toxicology, GMP manufacturing
  - Includes TLR, STING, and RIG-I agonists; nanoemulsions, proteins, carbohydrates, saponins, outer membrane vesicles (OMVs)
  - For use in infectious or immune mediated diseases; Opioid Use Disorder (vaccines targeting opioids)
- Several have entered clinical evaluation
  - 25+ clinical trials for allergy and infectious disease
- Used in COVID vaccines with approved status
  - Alhydroxiquim-II: TLR7/8 agonist; used in Covaxin
  - Advax-CpG: Novel carbohydrate plus TLR9 agonist; used in Spikogen

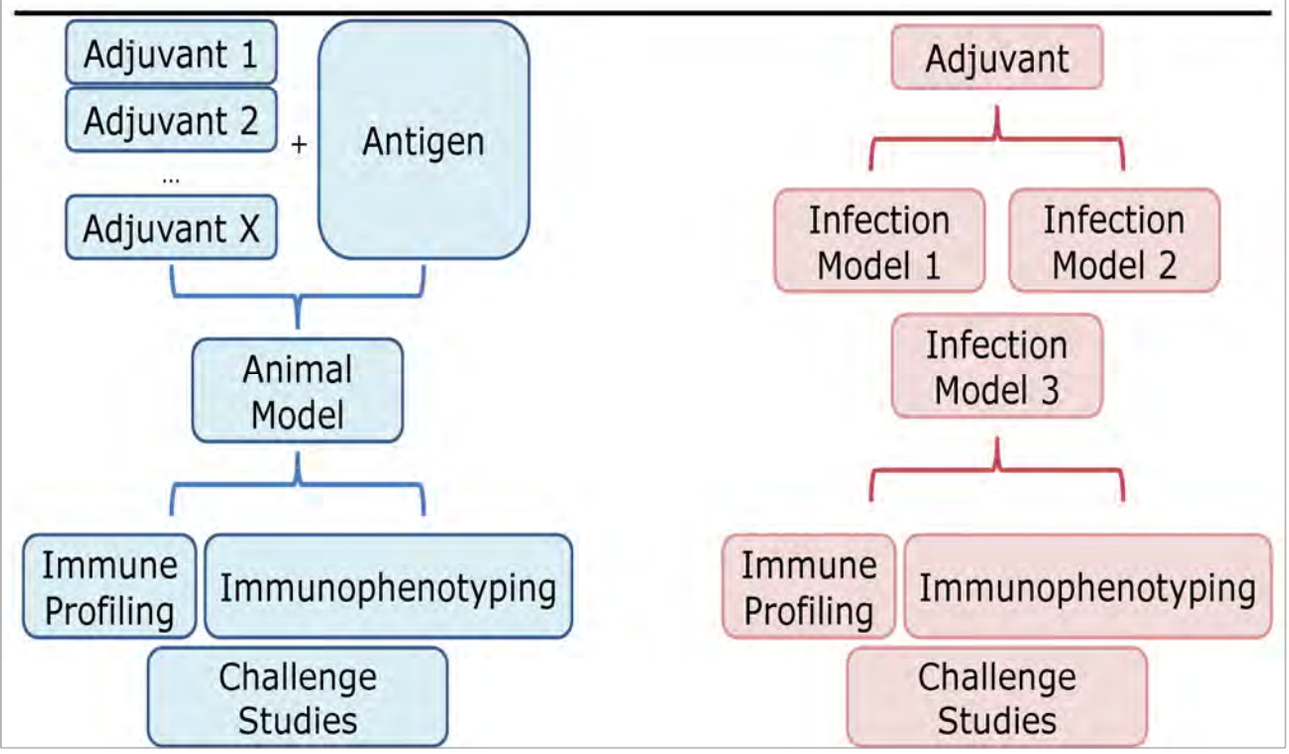
Adjuvant Development Program

	Advax	Advax-CpG55.2	NE01	dmLT	T-vant
Type	Carbohydrate	Carbohydrate + DNA	Emulsion	Recombinant protein	Outer Member Vesicle
Dev. Stage	Clinical trials	EUA	Clinical trials	Clinical trials	Clinical trial planned
MOA	Unknown	Unknown + TLR9 agonist	Unknown	GM1 ganglioside	Unknown
Vaccine Adjuvant Compendium	Link	Link	Link	Link	Link

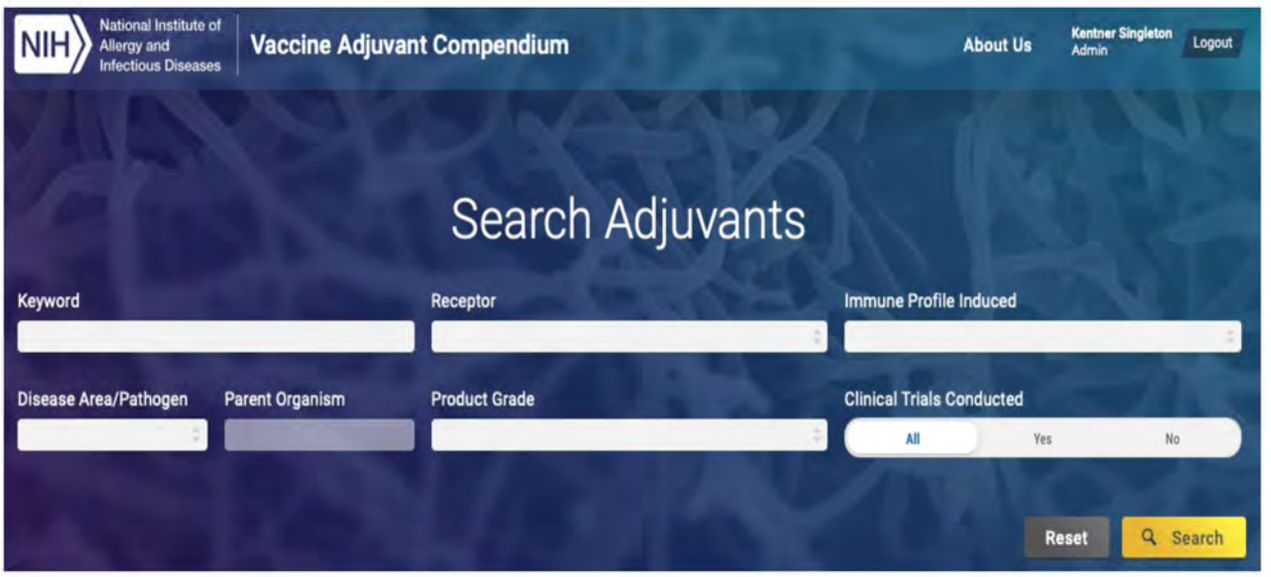
Adjuvant Development Program

	BECC	Alhydroxiquim-II	Fos47	TRAC478
Type	Synthetic phospholipid	Imidazoquinolinone	Small molecules	Synthetic + small molecule
Dev. Stage	Late pre-clinical	EUA	Clinical trial planned	Clinical trials planned
MOA	TLR4 agonist	TLR7/8 agonist	TLR4 and TLR7/8 agonists	TLR4 and TLR7/8 agonists
Vaccine Adjuvant Compendium	Link	Link	Link	Link

Adjuvant Comparison and Characterization



Adjuvants Available for Collaborations



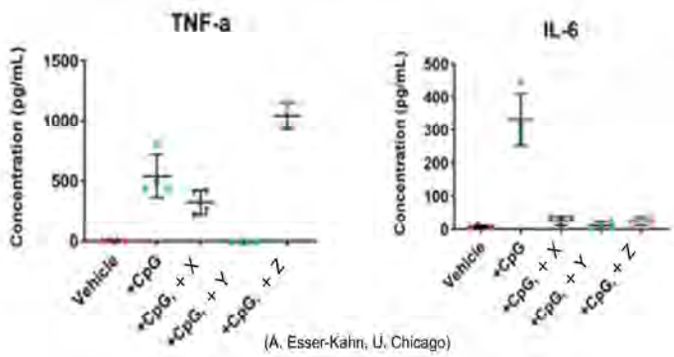
http://vac.niaid.nih.gov

Adjuvants Available for Collaborations

http://vac.niaid.nih.gov

Trends in Adjuvant Science

- Combination adjuvants (1+1=3)
- Adjuvant mimics
  - TLR4 agonist + Saponin
  - QS-21 alternatives
- Use of adjuvants with RNA vaccines
  - Genetic or chemical adjuvants
- Mucosal formulation and delivery
- Heterologous prime boost
- Uncoupling adjuvanticity and reactogenicity
- Adjuvants without immunostimulatory activity



(A. Esser-Kahn, U. Chicago)

Possible Paths for Collaboration

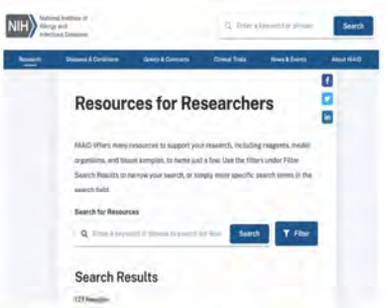
- Korean investigators may apply for most NIAID funding opportunities, directly or as collaborators
  - https://grants.nih.gov/grants/foreign/index.htm
- Joint meetings between Korean and US investigators
  - Joint scientific symposiums
  - Small in-country meetings
- Collaborative funding programs
  - NIH funds US scientists while KNIID supports Korean scientists on joint projects
- Adjuvant Webinar Series
  - https://www.niaid.nih.gov/research/adjuvant-webinar-series

NIAID Resources for Vaccine Adjuvants

https://tinyurl.com/2018Adjuvants

https://tinyurl.com/NIAID-Adjuvants

https://vac.niaid.nih.gov/



https://www.niaid.nih.gov/research/resources

3. The future of pandemic preparedness: Building collaborations and EV-D68 as a test case for NIAID/VRC's PREMISE program

Dr. Alicen Spaulding (NIAID, USA)

Alicen Burns Spaulding

Senior Advisor and Team Lead PREMISE

Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID)

- **EDUCATION:**

1999	English and Spanish, Wellesley College, BA,
2006	Social and Behavioral Sciences, Johns Hopkins University, Bloomberg School of Public Health, MPH
2013	Epidemiology (Biostatistics Minor), University of Minnesota, School of Public Health, PhD
2013 ~ 2015	Post-Doctoral Training, Presidential Management Fellowship

- **PROFESSIONAL EXPERIENCE:**

2000 ~ 2005	Health Extension Volunteer/Peace Corps Regional Recruiter, United States Peace Corps
2005 ~ 2010	Research Assistant/Research Coordinator
2010 ~ 2011	Program Evaluation Analyst, Minnesota Department of Health St. Paul
2010 ~ 2013	PhD Dissertation Research, University of Minnesota School of Public Health Minneapolis
2007 ~ 2013	Research Consultant, Cochrane Collaborative Review Group on HIV Infection and AIDS, UCSF San Francisco
2013 ~ 2015	Presidential Management Fellow, National Institutes of Health Bethesda
2015 ~ 2016	Epidemiologist, National Institute of Allergy and Infectious Diseases Bethesda
2016 ~ 2021	Scientific Investigator, Children's Minnesota Research Institute Minneapolis
2018 ~ Present	Affiliate Assistant Professor University of Minnesota School of Public Health Minneapolis

• PROFESSIONAL EXPERIENCE:

2021 - Present Senior Advisor and Team Lead

PREMISE, Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID)

• SUMMARY

Topic: The future of pandemic preparedness: Building collaborations and EV-D68 as a test case for NIAID/VRC's PREMISE program

Abstract

Dr. Spaulding will present on the experience of building PREMISE, a brand-new pandemic preparedness program at NIAID/VRC. This will include a discussion of how US and international partnerships are being built, what mechanisms for collaborations are being used, and examples of successful collaborations to date. She will then present on a study using EV-D68 as a test case for PREMISE, including an overview of the study design and current status. She will conclude by discussing how partners can engage with PREMISE and what some of the next strategic steps are for the program.

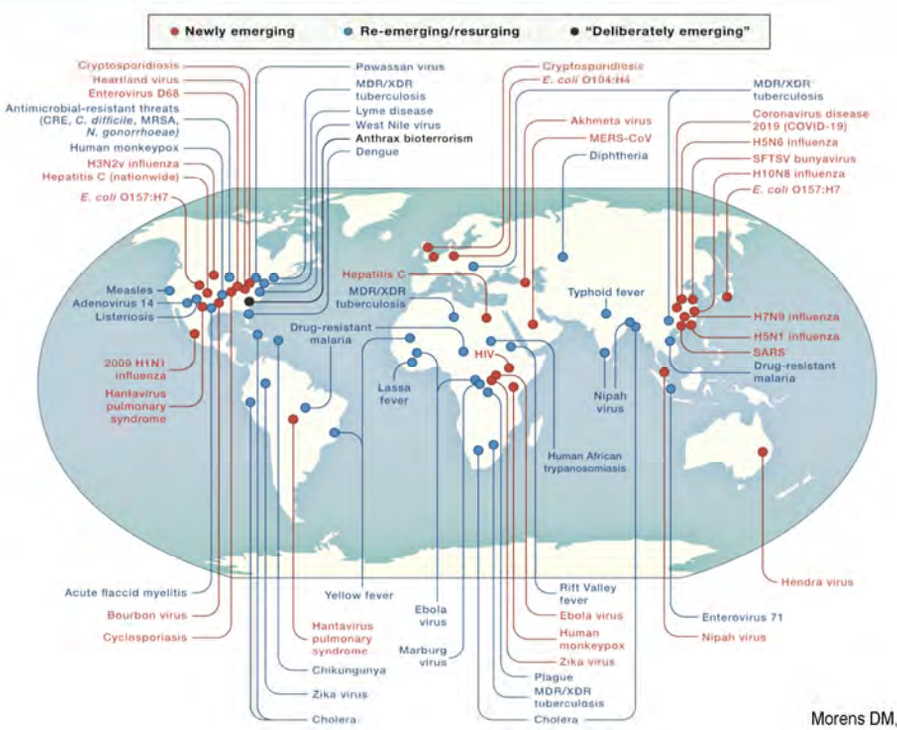
PREMISE
PANDEMIC RESPONSE REPOSITORY
MICROBIAL/IMMUNE SURVEILLANCE AND EPIDEMIOLOGY

NIH National Institute of Allergy and Infectious Diseases
Vaccine Research Center
Vaccines for Life™

The Future of Pandemic Preparedness: Building Collaborations and EV-D68 as a Test Case for NIAID/VRC's PREMISE Program

Alicen Spaulding, PhD, MPH
NIH/NIAID/VRC/PREMISE
February 22, 2023

Emerging Infectious Diseases

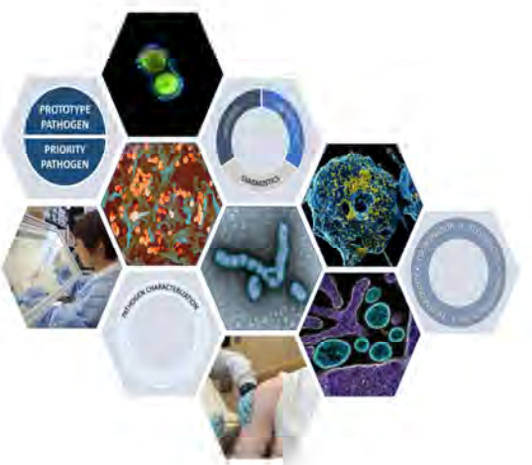


Morens DM, and Fauci AS, Cell 2020

NIAID Pandemic Preparedness Plan

The goals for the NIAID Pandemic Preparedness Plan are to:

- Systematically characterize pathogens of concern and increase research and surveillance to identify threats before they emerge
- Shorten timelines between pathogen emergence or outbreak onset and authorization/approval of candidate diagnostics and medical countermeasures, such as therapeutics and vaccines
- Bridge or eliminate existing gaps in research, infrastructure, and technology and expand preclinical and clinical testing capacity



NIAID Dec 2021

Next Steps for Pandemic Preparedness

- Given the 20+ years of VRC experience and relative readiness for CoVID-19 how can we best prepare for the next emerging virus epidemic or pandemic?
- Many strategies are established and have been launched or being discussed domestically and globally
- PREMISE is an anticipatory reagent and countermeasure program based at the VRC

PREMISE
PANDEMIC RESPONSE REPOSITORY
MICROBIAL/IMMUNE SURVEILLANCE AND EPIDEMIOLOGY

NIH National Institute of Allergy and Infectious Diseases
Vaccine Research Center
Vaccines for Life™

Building PREMISE

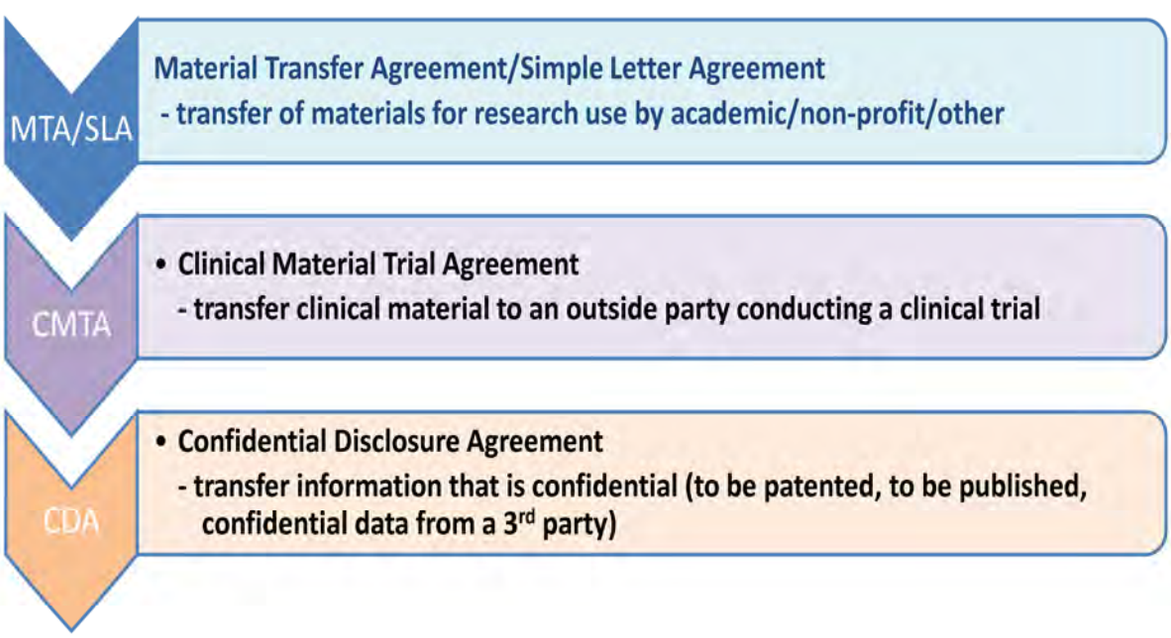
PREMISE is

- an immunology-based approach to pandemic preparedness
- pathogen-agnostic
- Focused extending virologic and immunologic screening to product discovery

PREMISE is not

- A global sero-surveillance network
- An early warning system to detect imminent pandemic threats
- A prototype pathogen approach to vaccine design

Types of Technology Transfer Agreements



Types of Technology Transfer Agreements

KNIID/PREMISE Collaboration

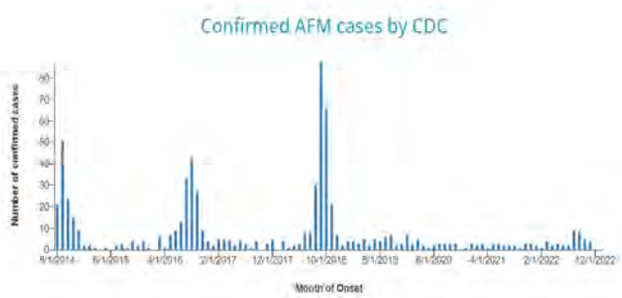
- Developing nAb against severe fever thrombocytopenia syndrome virus (SFTSV) in collaboration with:
  - Kyung-Chang Kim (Division Director, KNIID)
  - Hee-Young Lim (Staff Scientist, KNIID)
  - Hansem Li (Staff Scientist, KNIID)

- Apr 26, 2022: KNIID and PREMISE teams meet in person at NIH
- Summer 2022: Drafted research plan
- Oct 31, 2022: RCA executed
- Nov-present: Meetings and collaboration moving foward

EV-D68 as a Test Case for PREMISE

Background: EV-D68

- **EV-D68 is an emerging virus causing seasonal (late summer-fall), biennial outbreaks of respiratory disease since 2014**
- **Associated with polio-like paralysis cases of acute flaccid myelitis (AFM)**
  - Majority of children affected by EV-D68 AFM are left with persistent weakness and long-term disability
- **No known effective treatments, few vaccine candidates (pre-clinical)**



https://www.cdc.gov/acute-flaccid-myelitis/cases-in-us.html

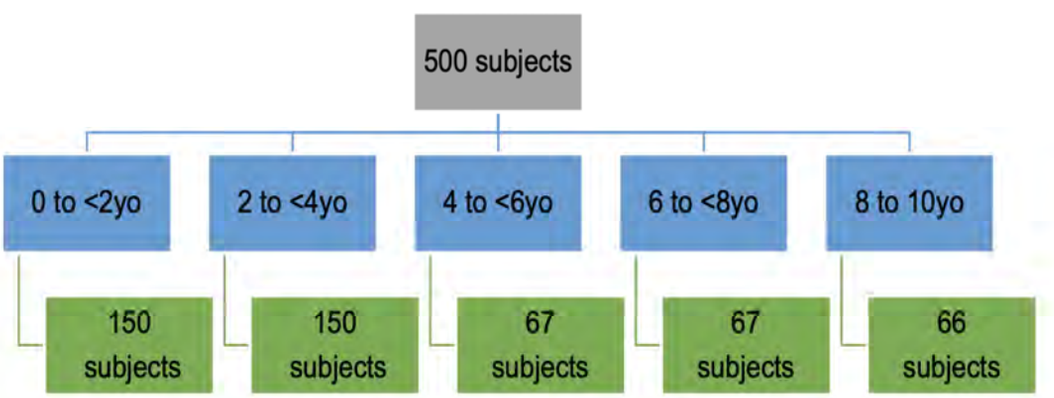
Enterovirus-D68 Study as a Test Case for PREMISE

- Prospective, observational pilot study to study EV-D68 epidemiology
- Enrolling 500 children ages 1-10, over 3 years, started Q1 2022:
  - Paired blood specimens collected pre-EV and post-EV season
  - Respiratory specimens during EV season illness
  - Immunologic screening for EV-D68 *plus* other childhood respiratory diseases and CoVs
  - Sequencing of respiratory specimens

- Enrollment sites:
  - U. Colorado: Kevin Messacar
  - U. North Carolina: Matthew Vogt
  - Weill Cornell: Perdita Permaul, Sallie Permar
  - U. Alabama: David Kimberlin
  - (Princeton: Bryan Grenfell and Jessica Metcalf for epidemiology)

- Recruitment to date:
  - 174 participants recruited with blood and respiratory sampling
  - August 2022: EV-D68 cases began to climb rapidly; CDC issued HAN

Study Design: Age Targets



Strategic Next Steps

- Executing new agreements
- Obtaining samples
- Designing and producing proteins from virus list
- Designing and making PhIP-seq libraries
- Developing additional custom assay plates
- Developing faster and higher-throughput platforms
- Developing virus discovery pipeline

Acknowledgements

PREMISE

- Danny Douek
- Leo Serebryannyy
- Sucheta Godbole
- Ananda Chowdhury
- Jenny Wang
- Megan Weitner
- Alex Mullens
- Jenny Bohl

VRC

- Karin Bok
- Lucio Gama

EV-D68 Study

- Kevin Messacar
- Matthew Vogt
- Perdita Permaul

Part 1. Antimicrobial resistance

Chair:
Shin-woo Kim, M.D., PhD.

1. One Health approach to antimicrobial resistance
Dr. Eun-Jeong Yoon (NIID, Korea)

2. One Health Antimicrobial Resistance research landscape in Singapore
Dr. Selina Poon (NCID, Singapore)

3. Population CPE evolution in Singapore
Dr. Ng Oon Tek (NCID, Singapore)

Part 1. Antimicrobial resistance

Moderator

Shin-Woo Kim

1) Vice president

The Korean Society for Antimicrobial Therapy

2) Professor

Kyungpook National University

- **EDUCATION:**

2004 ~ 2006	Gyunsang National University, Jinju, Korea (South) PhD
1992 ~ 1994	Kyungpook National University, Daegu, Korea (South) M.S
1990 ~ 1991	College of Medicine, Kyungpook National University M.D. licensed (Feb/1990)

- **PROFESSIONAL EXPERIENCE:**

2015 ~ Present	Professor of Infectious Diseases Kyungpook National University Hospital and Kyungpook National University
2005 ~ 2015	Associate Professor of Infectious Diseases Kyungpook National University Hospital and Kyungpook National University
2001 ~ 2005	Associate Professor of Infectious Diseases Kyungpook National University Hospital and Kyungpook National University
2000 ~ 2001	Clinical assistant Professor of Infectious Diseases
1998 ~ 2000	Clinical fellowship, Division of Infectious Diseases, Samsung Medical Center, Seoul, Korea
1991 ~ 1995	Residentship of Internal Medicine, Kyungpook National University Hospital
1990 ~ 1991	Internship, Kyungpook National University Hospital

1. One Health approach to antimicrobial resistance

Dr. Eun-Jeong Yoon (NIID, Korea)

Eun-Jeong YOON

Senior Staff Scientist

Division of Antimicrobial Resistance Research, NIID, KNIH, KDCA

• EDUCATION:

1999 ~ 2003	B.S. in Pharmacy, Ewha Woman's University College of Pharmacy
2003 ~ 2008	Ph. D. in Pharmacy, Seoul National University College of Pharmacy

• PROFESSIONAL EXPERIENCE:

2021 ~ Present	Senior Scientific Officer, Korea National Institute of Health, Korea Disease Control and Prevention Agency
2016 ~ 2021	Research Professor, Yonsei Univesity College of Medicine
2011 ~ 2016	Postdoc Researcher, Institut Pasteur, Paris
2009 ~ 2012	Scientific Officer, Ministry of Food and Drug Safety

• SUMMARY

Topic: One Health approach to antimicrobial resistance

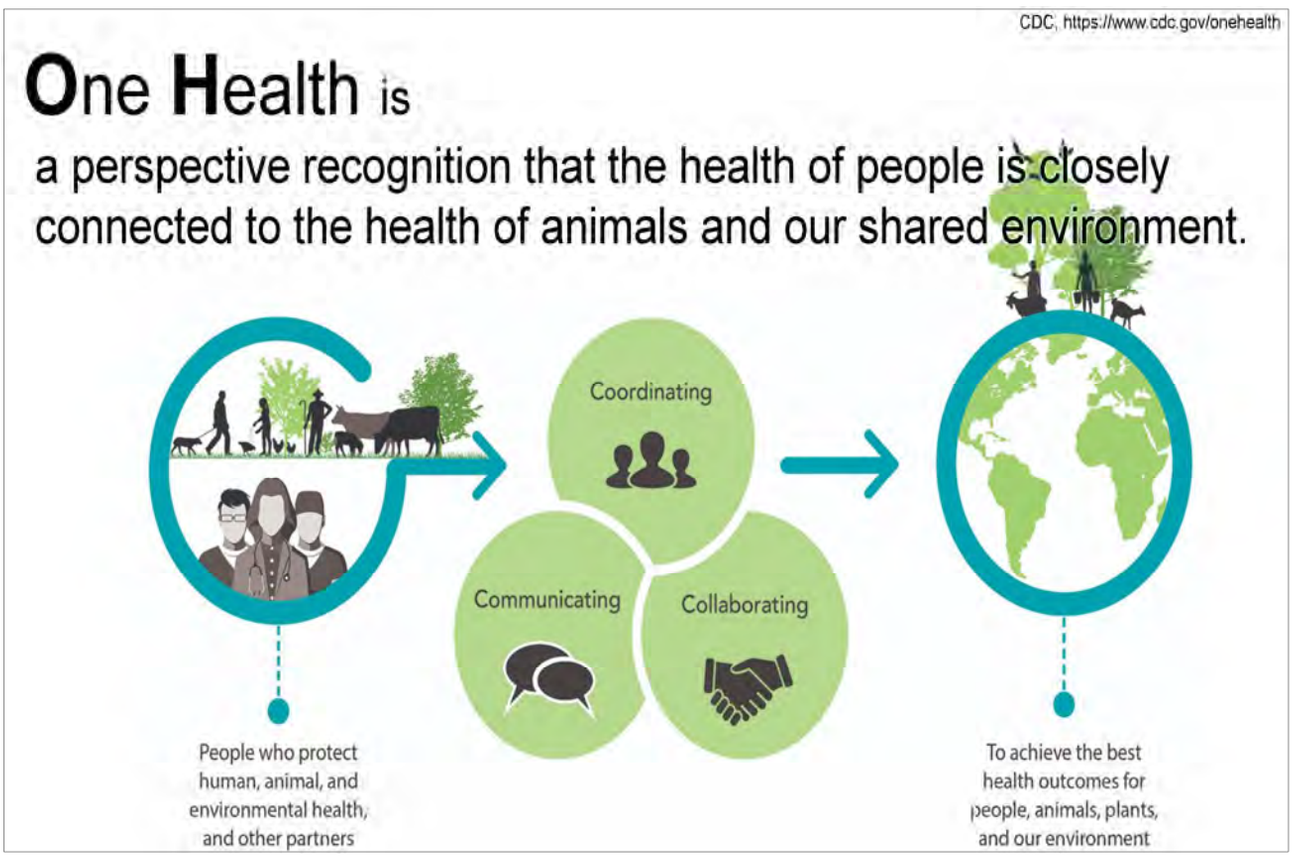
Abstract

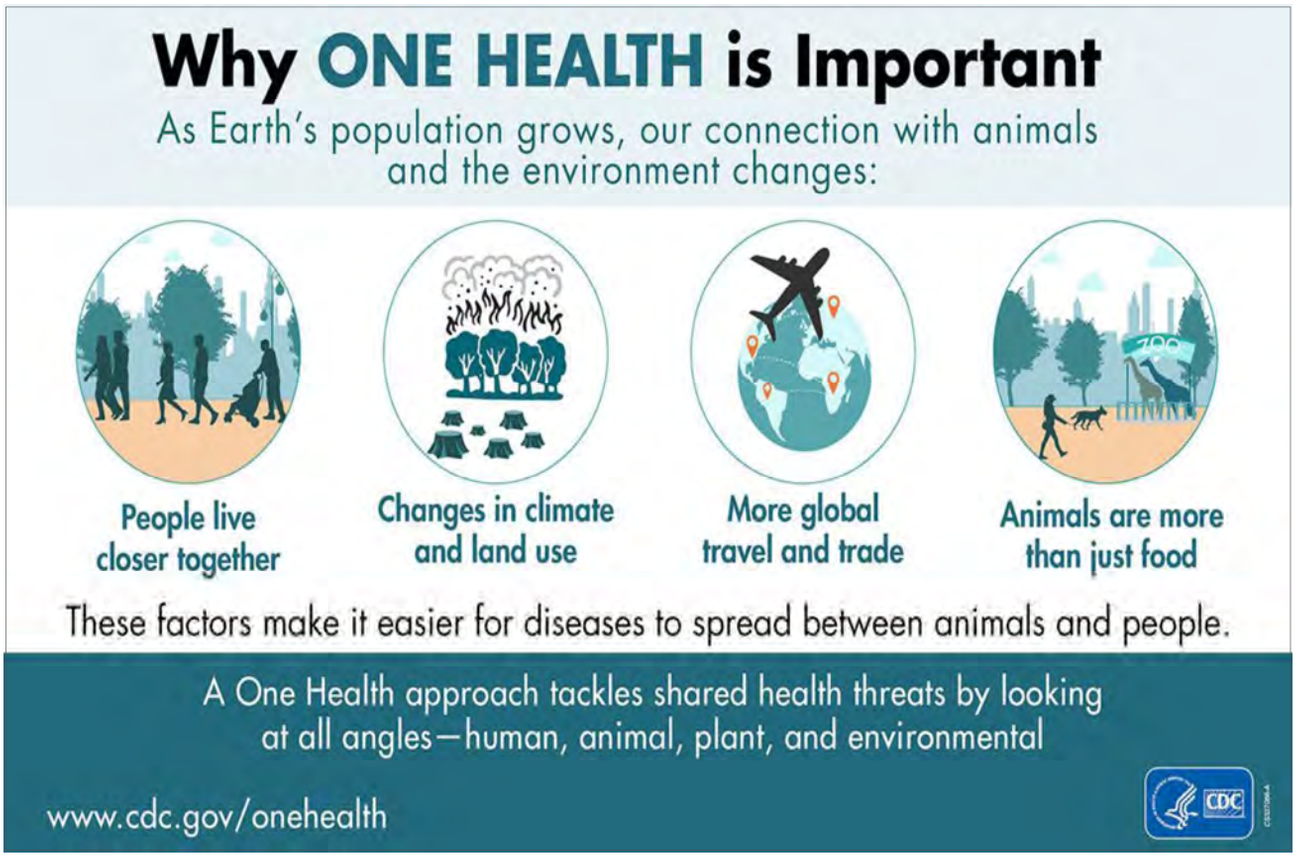
Antimicrobial resistance is considered to be one of the major threats to the public health because it significantly limits treatment options for bacterial infections. It has long been recognized that the antimicrobial resistance is an issue on our ecosystem affecting the health of human-animal-environment. Thus, it needs to address the antimicrobial resistance is by taking into account the complex nature through multisectoral approach, so called One Health. The One Health is a collaborative attempt to accomplish the public health by collective efforts of multiple professions in charge of the human-animal-environment health. In South Korea, after establishing the 1st National Action Plan on antimicrobial resistance in Aug. 2016, the Korea Disease Control and Prevention Agency (KDCA) initiated a pilot study for the One Health-based Antimicrobial Resistance Research

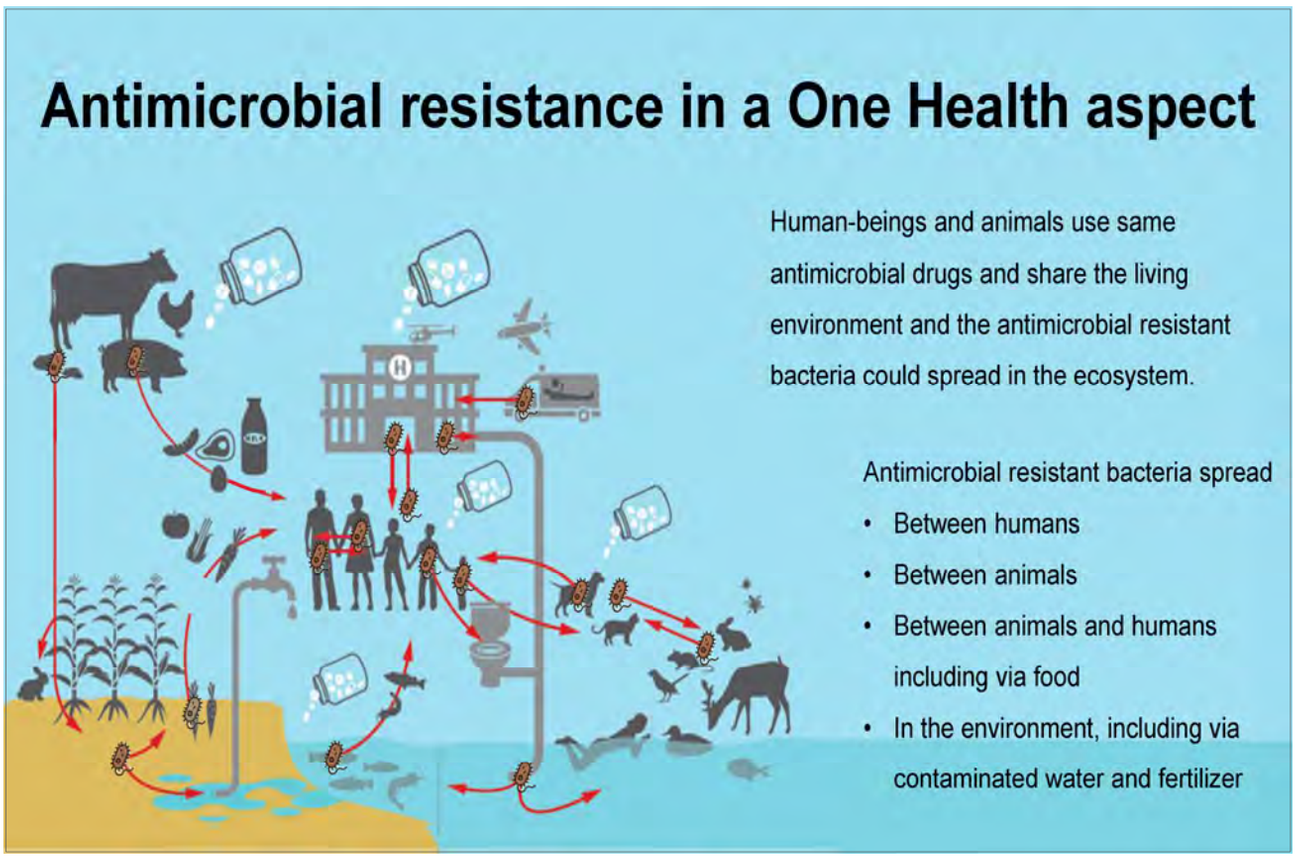
in 2017-2018. And the 5-year primary phase of the multi-sectoral joint project to One Health approach against AMR was started in 2019 based on the leadership of KDCA in collaboration with five other ministries, i.e. the Ministry of Science and Information and Communications Technology, the Ministry of Agriculture, Food, and Rural Affairs, the Ministry of Environment, the Ministry of Oceans and Fisheries, and the Ministry of Food and Drug Safety, for the mission to protect citizens from the harms of AMR. By 2021, the Korea Rural Development Administration participated in the project. Through the 4-year progression of the project, two major infrastructures were established, a portal system for One Health AMR and a multi-drug resistant bacterial isolate bank, and varied research projects are now conducting to understand i) the status of AMR dissemination in human-animal-environment sectors, ii) mechanisms of dissemination of the AMR through the One Health interphase, and iii) the way to stop the dissemination.

A One Health approach to antimicrobial resistance

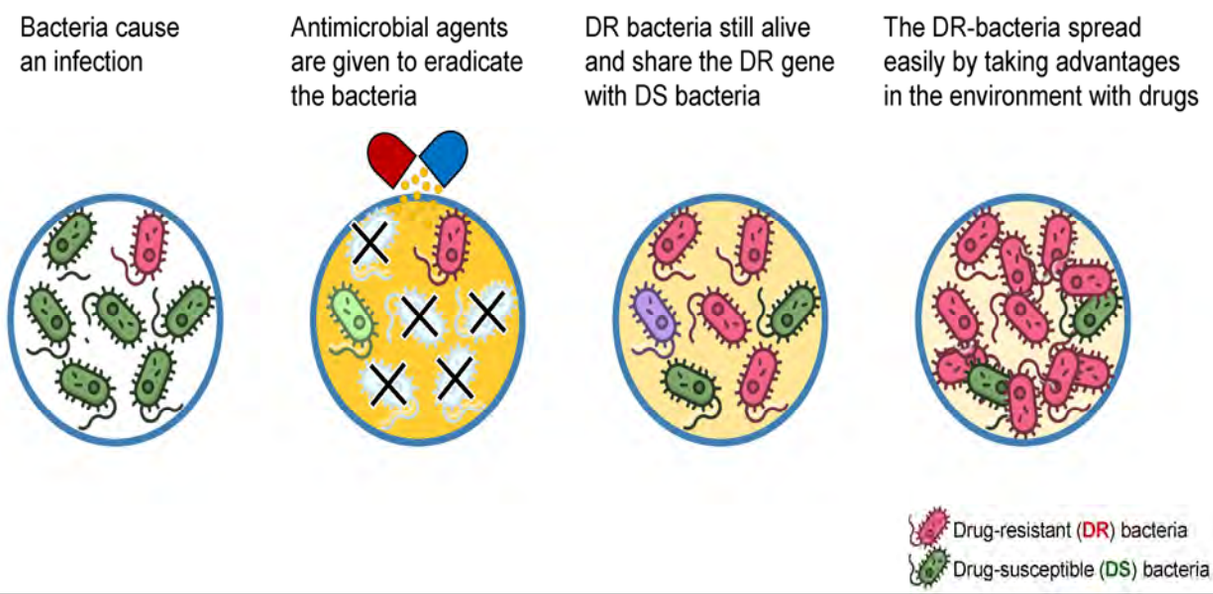
Eun-Jeong YOON R.Ph., Ph.D.
Division of Antimicrobial Resistance Research,
National Institute of Health, Korea Disease Control and Prevention Agency



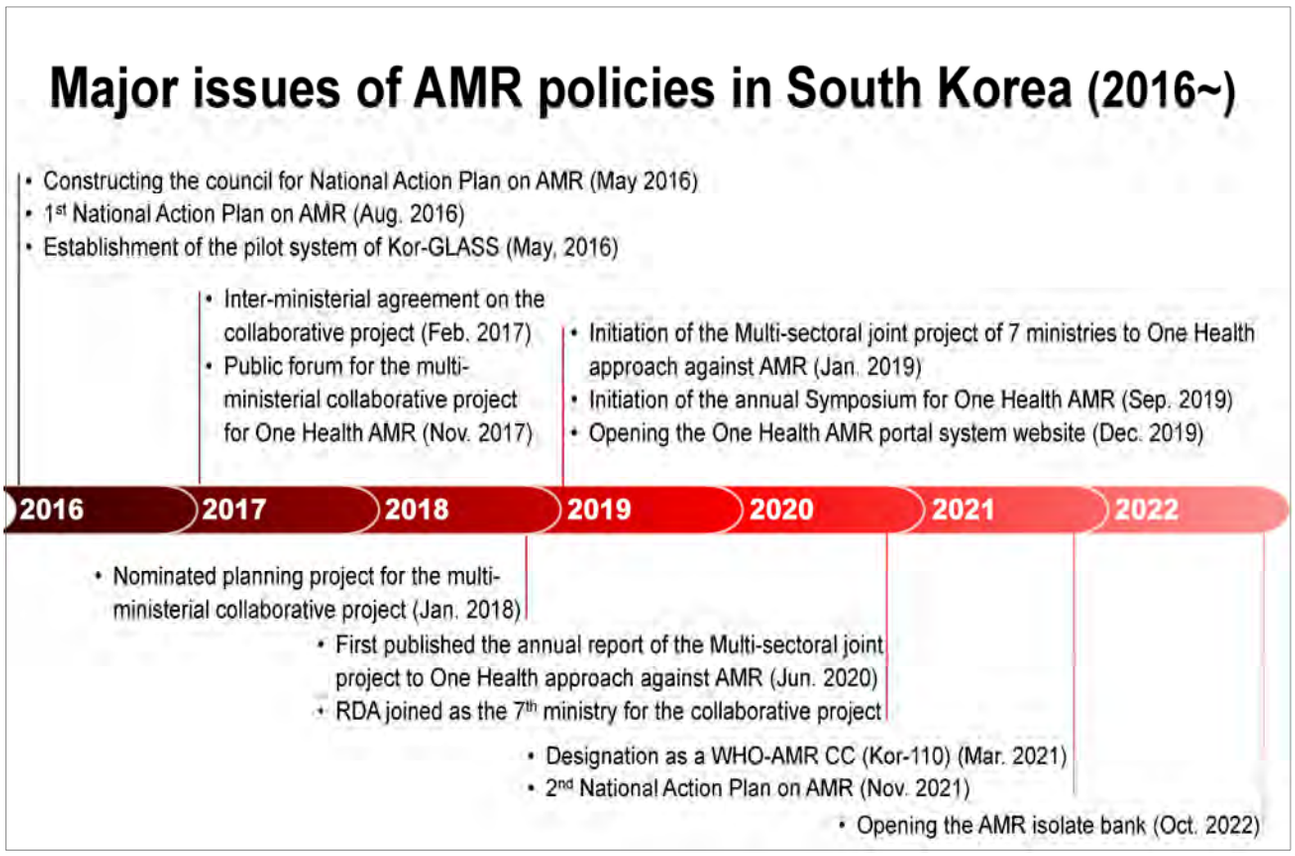

Why ONE HEALTH is Important
As Earth's population grows, our connection with animals and the environment changes:
People live closer together
Changes in climate and land use
More global travel and trade
Animals are more than just food
These factors make it easier for diseases to spread between animals and people.
A One Health approach tackles shared health threats by looking at all angles—human, animal, plant, and environmental
www.cdc.gov/onehealth
CDC

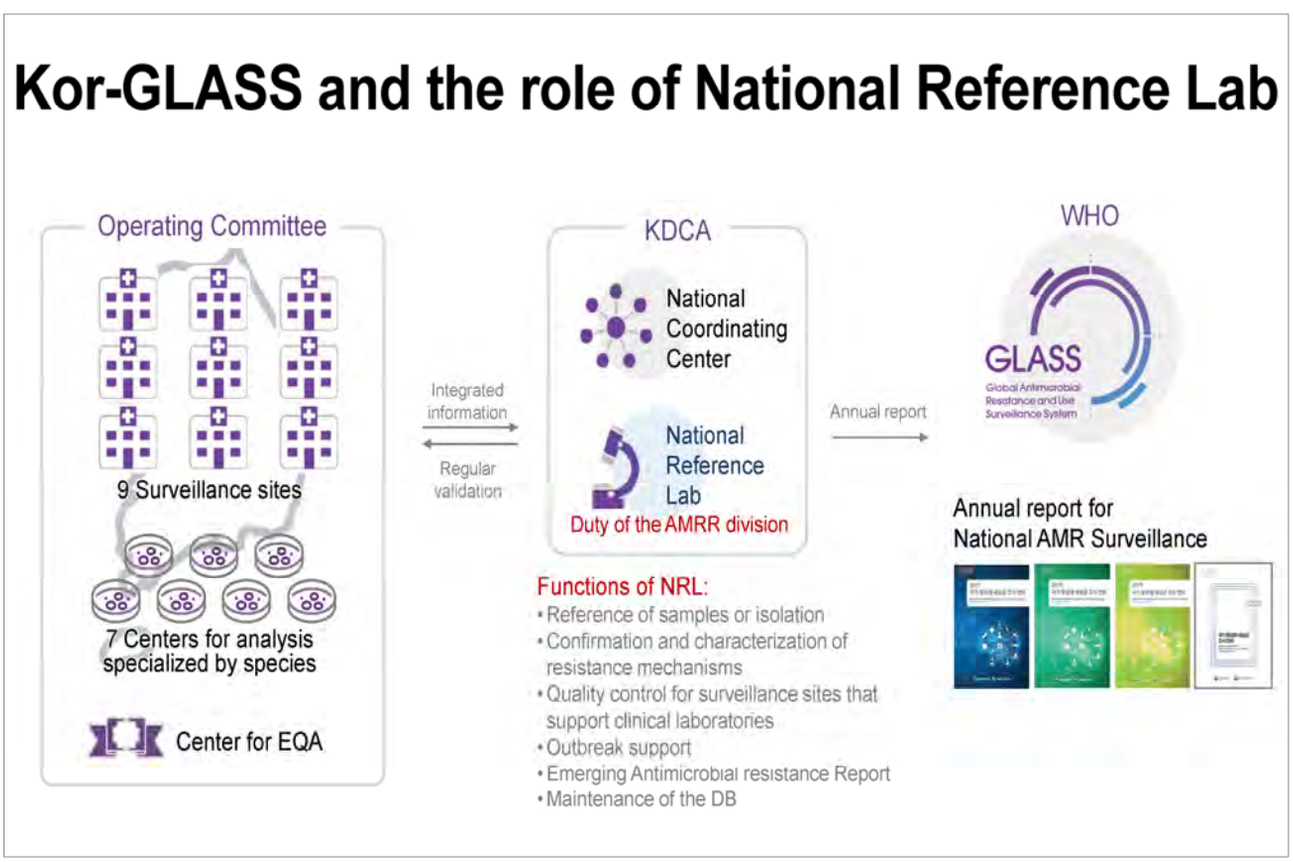

Antimicrobial resistance in a One Health aspect
Human-beings and animals use same antimicrobial drugs and share the living environment and the antimicrobial resistant bacteria could spread in the ecosystem.
Antimicrobial resistant bacteria spread
• Between humans
• Between animals
• Between animals and humans including via food
• In the environment, including via contaminated water and fertilizer

How the Antimicrobial Resistant bacteria occurs



To tackle the antimicrobial resistance using a One Health approach

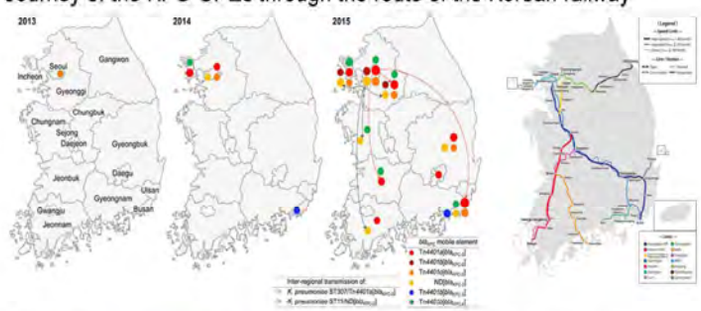

Major issues of AMR policies in South Korea (2016~)
• Constructing the council for National Action Plan on AMR (May 2016)
• 1st National Action Plan on AMR (Aug. 2016)
• Establishment of the pilot system of Kor-GLASS (May, 2016)
• Inter-ministerial agreement on the collaborative project (Feb. 2017)
• Public forum for the multi-ministerial collaborative project for One Health AMR (Nov. 2017)
• Initiation of the Multi-sectoral joint project of 7 ministries to One Health approach against AMR (Jan. 2019)
• Initiation of the annual Symposium for One Health AMR (Sep. 2019)
• Opening the One Health AMR portal system website (Dec. 2019)
2016
2017
2018
2019
2020
2021
2022
• Nominated planning project for the multi-ministerial collaborative project (Jan. 2018)
• First published the annual report of the Multi-sectoral joint project to One Health approach against AMR (Jun. 2020)
• RDA joined as the 7th ministry for the collaborative project
• Designation as a WHO-AMR CC (Kor-110) (Mar. 2021)
• 2nd National Action Plan on AMR (Nov. 2021)
• Opening the AMR isolate bank (Oct. 2022)


Kor-GLASS and the role of National Reference Lab
Operating Committee
9 Surveillance sites
7 Centers for analysis specialized by species
Center for EQA
Integrated information
Regular validation
KDCA
National Coordinating Center
National Reference Lab
Duty of the AMRR division
Annual report
WHO
GLASS
Global Antimicrobial Resistance and Use Surveillance System
Annual report for National AMR Surveillance
Functions of NRL:
• Reference of samples or isolation
• Confirmation and characterization of resistance mechanisms
• Quality control for surveillance sites that support clinical laboratories
• Outbreak support
• Emerging Antimicrobial resistance Report
• Maintenance of the DB

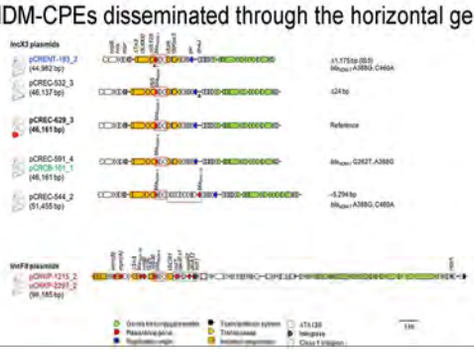
National Lab Surveillance System for CPE

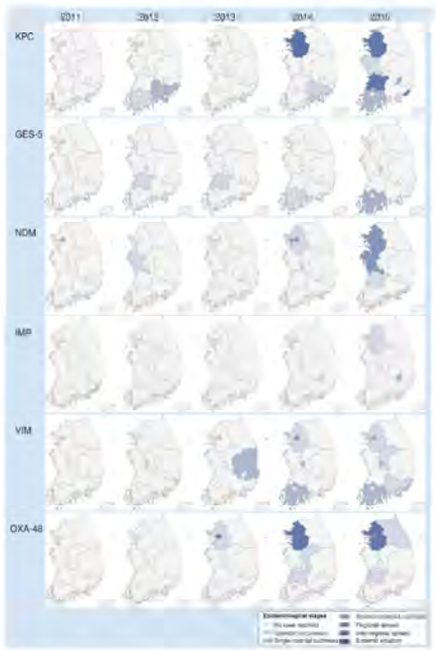
CPE epidemiology in South Korea

Journey of the KPC-CPEs through the route of the Korean railway



NDM-CPEs disseminated through the horizontal gene transfer

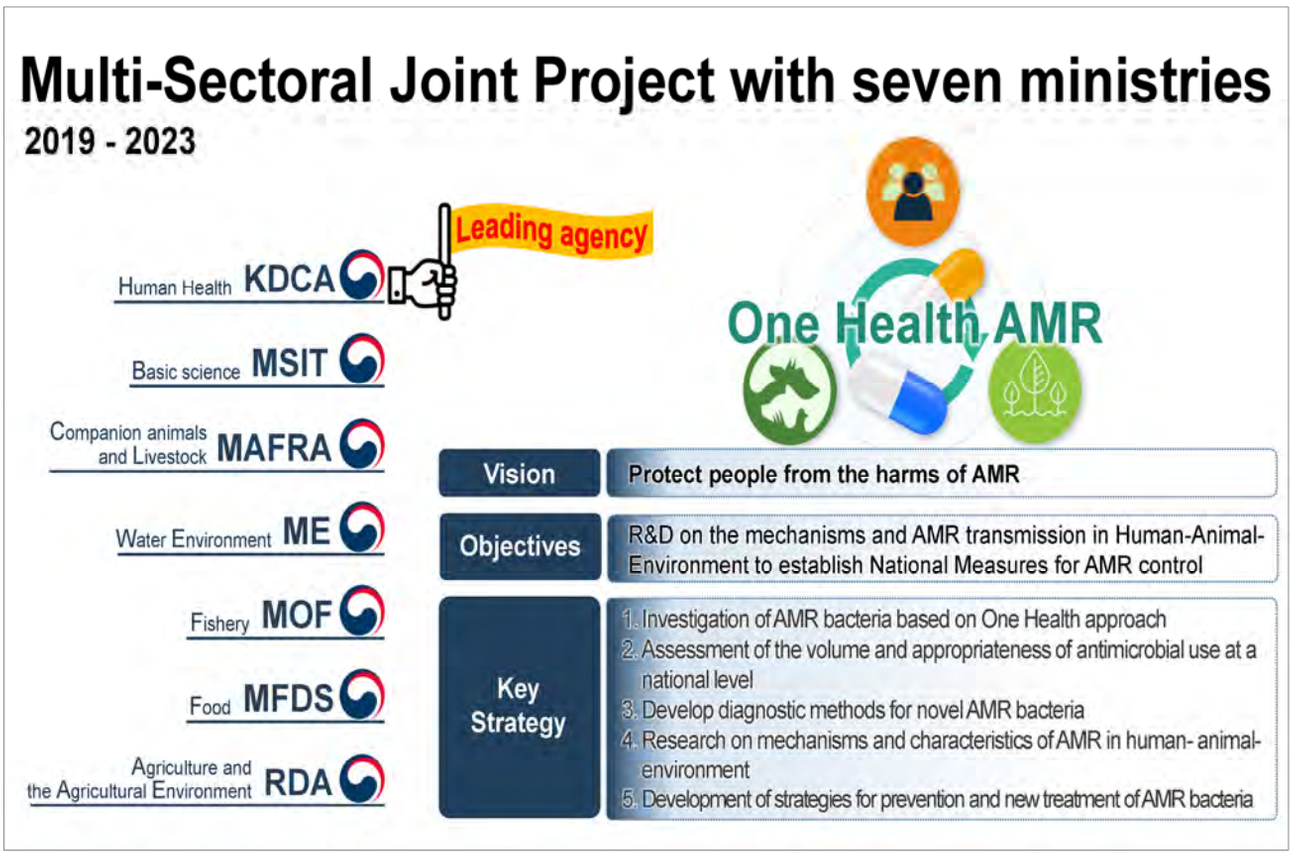


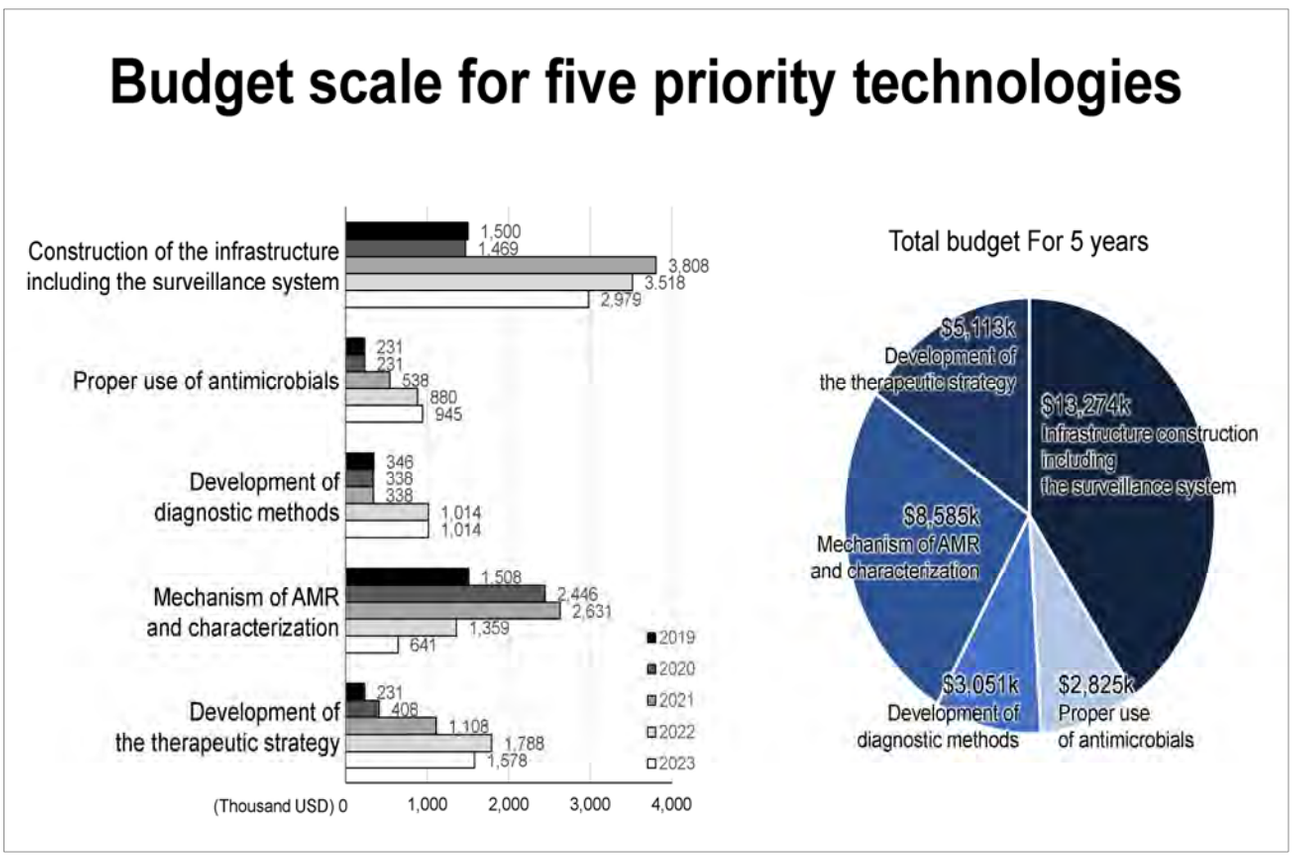


Yoon *et al.*, Frontiers in Microbiology 2018; Frontiers in Microbiology 2018; Future Microbiology 2018

3-phase plan for the One Health AMR project

Phase 1: 2019~2023	Phase 2: 2024~2028	Phase 3: 2029~2033
Constructing a solid foundation and the research infrastructure for One Health approach to cope with the AMR issue	Activating the AMR research using the One Health infrastructure and the integrated network for multi-sectoral cooperation	Advanced research and development for practical plan to countermeasure the AMR issue


Multi-Sectoral Joint Project with seven ministries
2019 - 2023
Leading agency
Human Health KDCA
Basic science MSIT
Companion animals and Livestock MAFRA
Water Environment ME
Fishery MOF
Food MFDS
Agriculture and the Agricultural Environment RDA
One Health AMR
Vision
Protect people from the harms of AMR
Objectives
R&D on the mechanisms and AMR transmission in Human-Animal-Environment to establish National Measures for AMR control
Key Strategy
1. Investigation of AMR bacteria based on One Health approach
2. Assessment of the volume and appropriateness of antimicrobial use at a national level
3. Develop diagnostic methods for novel AMR bacteria
4. Research on mechanisms and characteristics of AMR in human- animal-environment
5. Development of strategies for prevention and new treatment of AMR bacteria


Budget scale for five priority technologies
Construction of the infrastructure including the surveillance system
1,500
1,469
3,808
3,518
2,979
Proper use of antimicrobials
231
231
538
880
945
Development of diagnostic methods
346
338
338
1,014
1,014
Mechanism of AMR and characterization
1,508
2,446
2,631
1,359
641
Development of the therapeutic strategy
231
408
1,108
1,788
1,578
2019
2020
2021
2022
2023
(Thousand USD) 0
1,000
2,000
3,000
4,000
Total budget For 5 years
$5,113k
Development of the therapeutic strategy
$13,274k
Infrastructure construction including the surveillance system
$8,585k
Mechanism of AMR and characterization
$3,051k
Development of diagnostic methods
$2,825k
Proper use of antimicrobials

Major Infrastructures for the multi-sectoral joint project with 7 ministries

One Health AMR portal system

data

KDCA MSIT ME MAFRA MOF MFDS RDA

- National data for the rates of antimicrobial resistance
- National data for antimicrobial usage/sales
- Research subjects run by participating ministries

http://kdca.go.kr/nohas

Researchers and experts for Antimicrobial resistance in Bacteria

AMR isolate bank

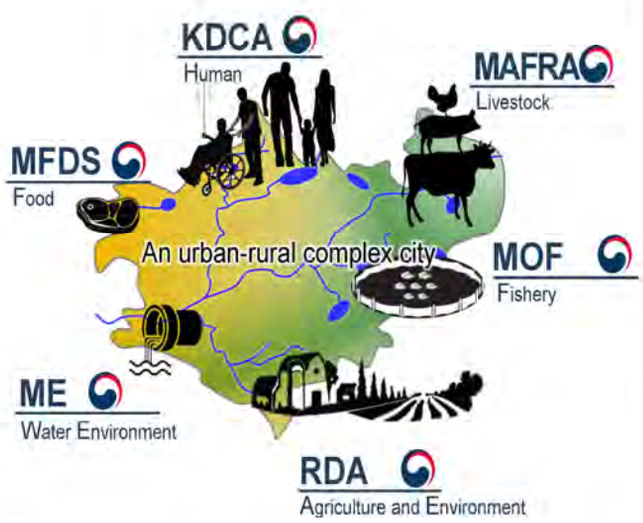
- 8,373 candidate isolates of 12 species
- **1,080 isolates of 9 species** are ready to be ordered

With	Antimicrobial susceptibility data Clinical information
Through	Standardized testing methods Standardized way of preservation Deposition

13

A pilot study to establish One Health AMR surveillance system ('21~'23)

Multi-sectoral One Health AMR surveillance study

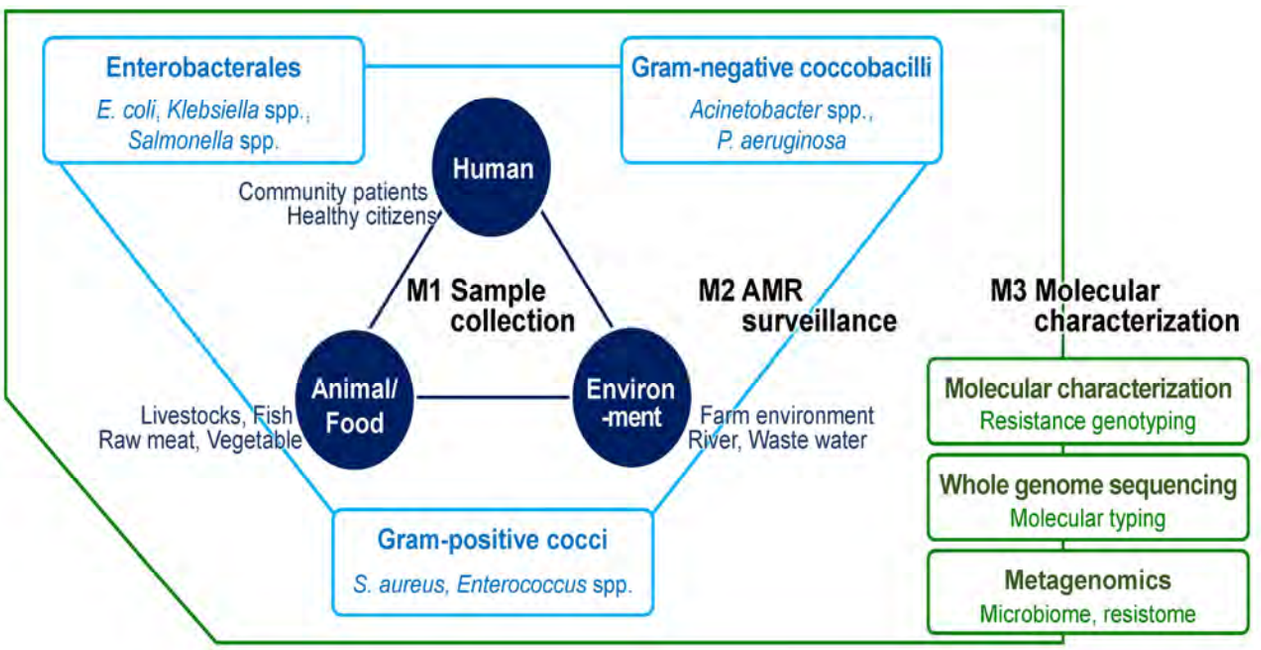


Collaboration w/	External experts on each sector and Government staff scientists
Target bacteria	*E. coli, Klebsiella* spp., *Salmonella* spp. *P. aeruginosa, Acinetobacter* spp. *S. aureus, Enterococcus* spp.
Isolated from	Patients in clinics, healthy citizens, livestock, vegetable, fish, raw meats, farm environments, river, waste water
Analyses by	Antimicrobial susceptibility testing Molecular epidemiology Whole genome sequencing Metagenomics including resistome

14

A pilot study to establish One Health AMR surveillance system ('21~'23)

Structure of the One Health AMR surveillance study



Advanced project for Multi-Ministral One Health AMR and control technology research 2024 - 2028

Leading agency

Human Health KDCA

Basic science MSIT

Companion animals and Livestock MAFRA

Water Environment ME

Fishery MOF

Food MFDS

Agriculture and the Agricultural Environment RDA

Vision	Ensure a firm health of Human-Animal-Environment through the secure technologies to control AMR
Objectives	- Constructing a sustainable One Health AMR surveillance system - Researching the technologies for the transmission intervention and inducing AMR
Key Strategy	**Advancing the multi-sectoral AMR surveillance system** - Advanding the Multisectoral reference lab for AMR and sustainable system for AMR surveillance - Advancing the infrastructure for multi-sectoral AMR **Researching the multi-sectoral AMR control and proper use of antimicrobials** - Developing the antimicrobial drugs, drug alternatives, and drug supplements - Developing the rapid diagnostic methods for AMR - Researching intervention methods to reduce the environmental AMR induction - Multi-sectoral manual preparation for proper use of antimicrobial drugs

Thank you for your attention

KDCA	http://kdca.go.kr
KNIH	http://www.nih.go.kr
KNIID	http://www.nih.go.kr/niid
One Health AMR portal	http://kdca.go.kr/nohas

17

2. One Health Antimicrobial Resistance research landscape in Singapore

Dr. Selina Poon (NCID, Singapore)

Selina POON

Manager

Antimicrobial Resistance Coordinating Office

National Centre for Infectious Diseases (NCID)

- **EDUCATION:**

2006	Bachelor of Science (Honours Biological Sciences, First Class)
2013	Doctor of Philosophy (Medical Science, Virology), Karolinska Institutet (Sweden)
2019	Master of Science, (Global Health Policy), London School of Hygiene And Tropical Medicine, University of London (UK)

- **PROFESSIONAL EXPERIENCE:**

2006 ~ 2007	Research Officer, Institute of Molecular and Cell Biology, A*STAR
2007 ~ 2008	Research Officer, Systems Biology, Genome Institute of Singapore, A*STAR
2008 ~ 2009	Visiting Scholar, Department of Molecular and Cellular Biology, University of California, Davis, USA
2008 ~ 2012	Doktorand (PhD Candidate), Karolinska Institutet, Sweden

- **SUMMARY**

Topic: One Health AMR research landscape in Singapore

Abstract

In this session, Dr Poon will share the findings of a review of Singapore's antimicrobial resistance research landscape (2009-2019) conducted by AMRCO, and discuss the areas of research needs that were identified from the review.

3. Population CPE evolution in Singapore

Dr. Ng Oon Tek (NCID, Singapore)

NG Oon Tek

1. Senior Consultant

i. National Centre for Infectious Diseases (NCID)

ii. Department of Infectious Disease, Tan Tock Seng Hospital

2. Associate Professor,

Lee Kong Chian School of Medicine, Nanyang Technological University

- **EDUCATION:**

2000	MBBS, National University of Singapore.
2004	MRCP / Mmed (Internal Medicine)
2008	Infectious Diseases Specialist, Singapore Medical Council
2010	Master Public Health, Johns Hopkins Bloomberg School of Public Health

- **PROFESSIONAL EXPERIENCE:**

2005 ~ 2008	Registrar, TTSH
2008 ~ 2010	Associate Consultant, TTSH
2010- ~ 2016	Consultant, Institute of Infectious Disease and Epidemiology, TTSH
2010 ~ 2011	Postdoctoral Fellowship, School of Medicine, Johns Hopkins Medical Institutions
2012 ~ 2017	Adjunct Assistant Professor, Saw Swee Hock School of Public Health, NUS
2016 ~ 2019	Assistant Professor, Lee Kong Chian School of Medicine, NTU
2017 ~ 2019	Senior Consultant, Communicable Disease Division, MOH, Singapore
2016 ~ current	Senior Consultant, NCID, Singapore

- **SUMMARY**

Topic: Population CPE evolution in Singapore

Abstract

In this session A/Prof Ng will discuss follow-up work to the recently published CaPES analysis of CPE transmission in Singapore over 5 years. The genomic core of CaPES has closed 1,000 genomes and results from this high resolution analysis will be discussed in this session

Part 2. Long COVID-19

Chair:
Jun-yong Choi, M.D., PhD.

1. Long COVID Research Projects in NIID

Dr. So-Young Lee (NIID, Korea)

2. Long COVID treatment trials: pathogenesis guides intervention

Dr. David Lye (NCID, Singapore)

Part 2. Long COVID-19

Moderator

Jun-Yong Choi

Professor

Yonsei University College of Medicine, Seoul, Republic of Korea

- **EDUCATION:**

2003 ~ 2005	Research Fellow in Division of Infectious Diseases, Severance Hospital
2002 ~ 2005	Department of Medicine, the Graduated School, Yonsei University (Ph.D.)
2000 ~ 2002	Department of Medicine, the Graduated School, Yonsei University (Master's Degree)
1992 ~ 1998	Yonsei University College of Medicine, Seoul, Korea (Bachelor's Degree)

- **PROFESSIONAL EXPERIENCE:**

2017 ~ Present	Professor, Department of Internal Medicine, Yonsei University College of Medicine
2014 ~ 2020	Director, Infection Control Office, Severance Hospital
2013 ~ 2019	Chief, Division of Infectious Diseases, Severance Hospital
2012 ~ 2017	Associate Professor, Department of Internal Medicine, Yonsei University College of Medicine
2008 ~ 2012	Assistant Professor, Department of Internal Medicine, Yonsei University College of Medicine
2009 ~ 2011	Visiting Scholar, Center for AIDS Research, University of Califonial San Diego
2005 ~ 2008	Faculty Instructor, Department of Internal Medicine, Yonsei University College of Medicine

Part 2
Long COVID-19

1. Long COVID Research Projects in NIID

Dr. So-Young Lee (NIID, Korea)

So-Young Lee

Acting Division Director

Clinical Research Division, NIID

- **EDUCATION:**

2001 ~ 2006	Ph.D. in Neurophysiology, Pohang University of Science and Technology (POSTECH), Korea

- **PROFESSIONAL EXPERIENCE:**

2021 ~ Present	Senior Scientific Officer/Acting Division Director Clinical Research Division, NIID, NIH, Korea
2012 ~ 2021	Senior Scientific Reviewer Cell and Gene Therapy Product Division, MFDS (Ministry of Food and Drug Safety), etc, Korea
2011 ~ 2012	Research Professor Department of Bio and Brain Engineering, KAIST, Korea
2008 ~ 2011	Postdoctoral Research Fellow School of Medicine, Tufts University, USA
2006 ~ 2008	Postdoctoral Research Fellow School of Medicine, University of Pennsylvania, USA

- **SUMMARY**

Topic: What we are learning about long COVID: Long COVID Research Projects in NIID

Abstract

I will share the definition of long COVID-19 in Korea and discuss future plans of the long COVID research project through summarizing previous research cases that have been conducted in Korea using cohorts of COVID-19 patients and health insurance big data.

1. Organization and Responsibilities
2. Clinical Research
3. Long COVID Studies
4. Definition of Long COVID in Korea
5. Long COVID Research Project

So-Young Lee, Ph.D.

Acting Division Director
Clinical Research Division
Center for Emerging Virus Research, NIID

01. Organization & Responsibilities

The total budget of infectious diseases R&D is ₩ 67.4 billion (~ $48M) and ₩ 84.8 billion (~$61M), in 2021 and 2022, respectively.
175 Employees are currently conducting researches.

National Institute of Health

01. Organization & Responsibilities

01. Organization & Responsibilities Center for Emerging Virus Research

Vision

Establish control strategy on national infectious disease via development of diagnostics, therapeutics for Emerging and Acute/Chronic viral diseases.

Mission

Develop core technology for virus infection diagnostics, treatment and immunity and establish a system for practical application.

Division of Emerging Virus & Vector Research	Division of Acute Viral Diseases	Division of Chronic Viral Diseases	Division of Clinical Research
Development of therapeutics, and support commercialization for emerging virus infectious diseases such as COVID-19	Development of control technology by way of treatments and immune responses against respiratory & vector-borne virus diseases	AIDS therapeutic(cure) drug development	Planning & Support for clinical research on infectious diseases
Establish a platform for development and evaluation of antiviral agent, as of drug repositioning	Establishment of a new infection model to develop and to evaluate control technology against enteric virus infection	Chronic hepatitis(type B/C) therapeutic(cure) drug development	Operation & Management of infectious disease cohort
Develop research platform and control technology responding to high risk virus infections such as Ebola, Nipah	Establishment of acute virus research infrastructures to secure resources through domestic and global cooperation	Practical use of AIDS and chronic hepatitis treatment	Conducting translational research on infectious disease
Establish research networks & advanced infrastructure for emerging virus research through internal and external cooperation			

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02. Clinical Research

COVID-19

- ✓ Clinical Studies
  Evaluating the clinical effectiveness of a treatment for COVID-19 patients
  Evaluating the clinical aspects in patients infected with SARS-CoV2 variants
  Evaluating the clinical aspects and the underlying mechanisms of post-COVID-19 conditions
  Analyzing risk factors for progression to severe disease using COVID-19 big data
  etc
- ✓ Clinical Trials
  K-COT-1(Camostat + Remdesivir)
  STRIVE for inpatients, collaborating with US NIAID

Chronic infectious disease

- ✓ **Cohort studies**
  HIV/AIDS, HCV, HPV, HBV, TB

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03. Long COVID Studies

Initial Studies

- ✓ Studies using COVID19 patients cohorts
- ✓ Studies using public big data
- ✓ National Health Survey
  (Korea National Health and Nutrition Examination Survey, Community Health Survey)

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03-1. Cohort Studies of COVID-19 Patients

Study #1

RESEARCH Open Access

Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea

Yoonjung Kim, Bitna-Ha, Shin-Woo Kim*, Hyun-Ha Chang, Ki Tae Kwon, Sohyun Bae and Soyoon Hwang

Ref. Kim et al., BMC Infectious Diseases (2022) 22:93

A prospective online survey was conducted on recovered patients who were previously diagnosed with COVID-19 between Feb 2020 and Mar 2020 at Kyungpook National Univ. Hospital.
Overall, 900 and 241 responders were followed up at 6 and 12 months after recovery from COVID-19 in the first and second surveys, respectively.

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03-2. Cohort Studies of COVID-19 Patients

Study #1

RESEARCH Open Access

Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea

Yoonjung Kim, Bitna-Ha, Shin-Woo Kim*, Hyun-Ha Chang, Ki Tae Kwon, Sohyun Bae and Soyoon Hwang

Ref. Kim et al., BMC Infectious Diseases (2022) 22:93

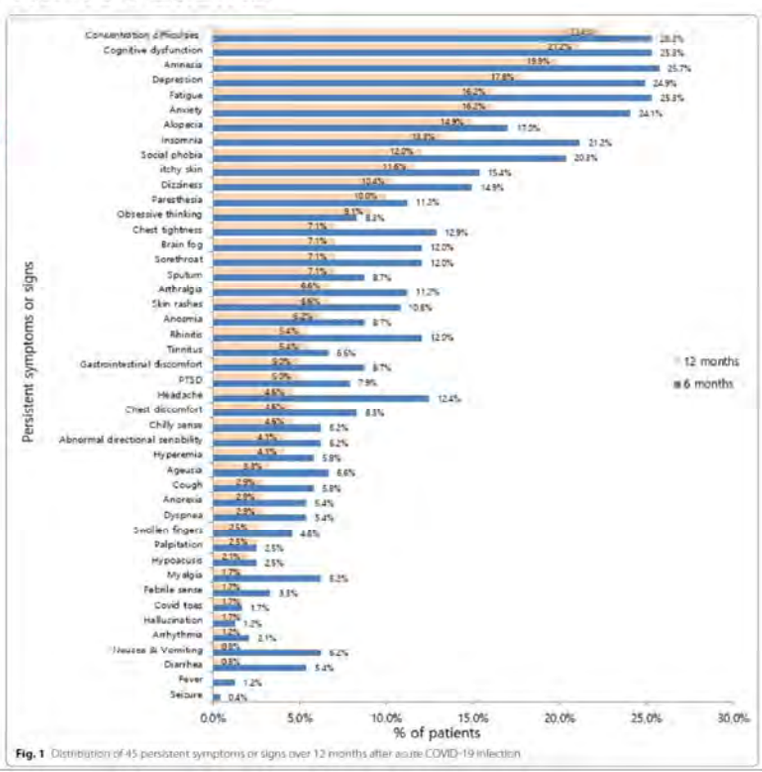

Fig. 1 Distribution of 45 persistent symptoms or signs over 12 months after acute COVID-19 infection

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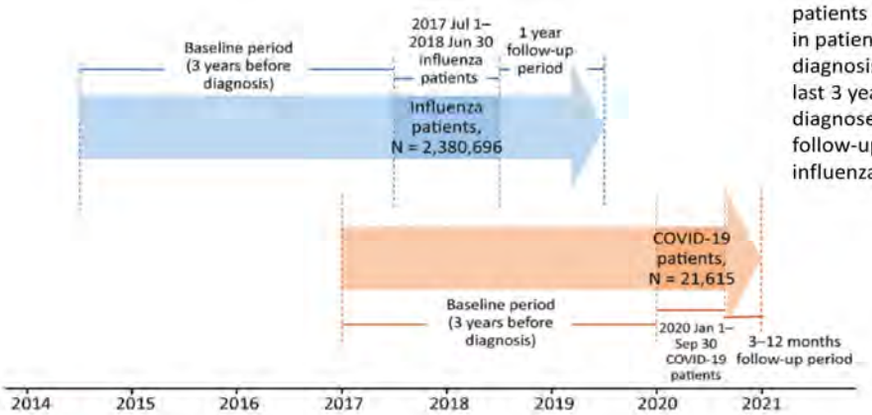
03-3. Studies using Public Big Data

Study #2

Comparison of Complications after Coronavirus Disease and Seasonal Influenza, South Korea

Hyejin Lee,[1] Ho Kyung Sung,[1] Dokyoung Lee,[1] Yeonmi Choi, Ji Yoon Lee, Jin Yong Lee,[2] Myoung-don Oh[2]

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 28, No. 2, February 2022



Complication for COVID-19 and influenza patients were defined as signs or symptoms in patients who had not received a diagnosis of those specific conditions in the last 3 years but who received new diagnoses of complications during the follow-up period after COVID-19 or influenza diagnosis.

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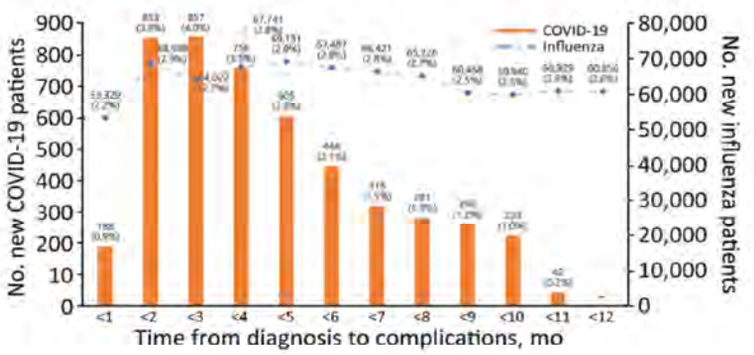
03-4. Studies using Public Big Data

Study #2

Comparison of Complications after Coronavirus Disease and Seasonal Influenza, South Korea

Hyejin Lee,[1] Ho Kyung Sung,[1] Dokyoung Lee,[1] Yeonmi Choi, Ji Yoon Lee, Jin Yong Lee,[2] Myoung-don Oh[2]

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 28, No. 2, February 2022



Among all COVID-19 patients, 4,139 (19.1%) had >1 complications after their diagnosis, and 678,845 (28.5%) of influenza patients had >1 complications after their diagnosis.

COVID-19 complications typically occurred 2–3 months after diagnosis.

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03-5. Studies using Public Big Data

Study #3

RESEARCH LETTER

Association Between Vaccination and Acute Myocardial Infarction and Ischemic Stroke After COVID-19 Infection

Ref. Kim YE et al., JAMA (2022) 328(9): 887-889

Table 2. Risk for Cardiovascular Events by Vaccination Status

	No. of events		Incidence per 1 000 000 person-days			
	Not vaccinated (n = 62 727)	Fully vaccinated (n = 168 310)	Not vaccinated	Fully vaccinated	Adjusted HR (95% CI)	*P* value
Composite outcome	31	74	6.18	5.49	0.42 (0.29-0.62)	<.001
Acute myocardial infarction	8	24	1.60	1.78	0.48 (0.25-0.94)	.03
Ischemic stroke	23	50	4.59	3.71	0.40 (0.26-0.63)	<.001

Adults aged 18 years or older who were diagnosed with COVID-19, including asymptomatic infections, between July 2020 and December 2021 were included.
Of 592 719 patients with COVID-19 during the study period, 231037 patients were included, of whom 62 727 were never vaccinated and 168 310 were fully vaccinated.

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03-6. Studies using National Survey

Study #4 (Press Release by Korea CDC on Jan 19, 2023) - Provisional Results

- ✓ National Health and Nutrition Examination Survey: A total of 3,915 people participated from June 6, 2022 to Dec 22, 2022.
- ✓ Community Health Survey: A total of 231,785 people participated from Aug 16, 2022 to Nov 7, 2022.

	National Health and Nutrition Examination Survey (≥ 1 year old)	Community Health Survey (≥ 19 years old)
Experienced symptoms for 4 weeks or longer	24.7% Female 30.7% > Male 16.1%	19.9% Female 24.7% > Male 14.2%
Types of symptoms that last more than 4 weeks	Cough, sputum, fatigue, sore throat in order	Cough, sputum, fatigue, sore throat in order
Treatment of symptoms lasting more than 4 weeks	Outpatient treatment 35.6% Pharmacy visit 6.6% No treatment 56.9%	Outpatient treatment 45.2% Pharmacy visit 15.8% No treatment 37.0%
Whether daily life is hindered by symptoms lasting more than 4 weeks	A little 53.1% A lot 15.0%	A little 59.7% A lot 18.1%
Proportion of experiencing symptoms following vaccination	Not vaccinated 44.8% > Fully vaccinated 30.0%	Not vaccinated 23.4% > Fully vaccinated 19.7%

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03-7. Long COVID Studies - Summary

- ✓ Based on the National Survey data, persistent symptoms at least for 4 weeks after acute COVID-19 are observed in about 20% of confirmed cases.
- ✓ Long COVID is most commonly occur within 3 months after acute phase, and improves over time, however, neurocognitive symptoms can last longer than other symptoms even after 1 year.
- ✓ Follow-up studies are needed to explore the effects of viral mutations, major symptoms requiring treatment, their diagnosis, and treatment strategies.

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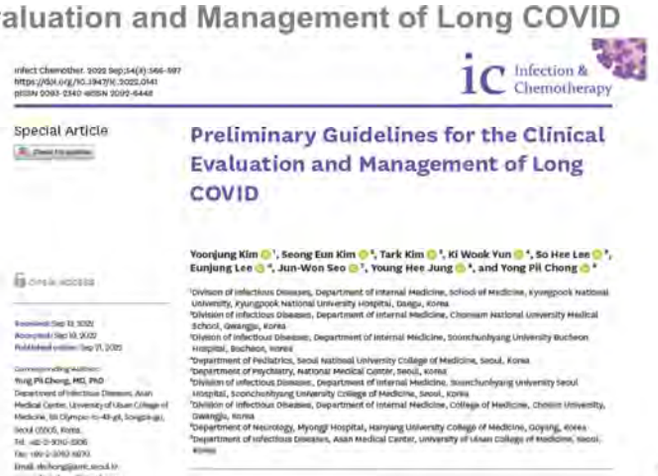
04. Definition of Long COVID in Korea

Definition

- ✓ Long COVID is defined as the presence of **symptoms/signs that persist after 12 weeks that cannot be explained by other diseases**.

Preliminary Guidelines for clinical Evaluation and Management of Long COVID

- ✓ published in July 2022
- ✓ under the supervision of the Korean Society of Infectious Diseases


Infection & Chemotherapy

Special Article

Preliminary Guidelines for the Clinical Evaluation and Management of Long COVID

National Institute of Health

05. Long COVID Research Project

Aims	1. Providing a scientific basis for Long COVID-19 Management 2. Establishing research infra for future infectious diseases
Objects	Investigating and researching the incidence rate, symptoms, risk factors, and causes, etc through a cohort study including children and adolescents
Contents	**Part I** ◦ A Cohort-based study on long COVID-19 ◦ Treatment guidelines **Part II** ◦ DB and other big data-based study on long COVID-19 • DB will be built with the data collected in Part I and Part III. **Part III** ◦ Translational research on long COVID-19

- ✓ The Budget to conduct this Long COVID-19 research Project has finalized on May 29, 2022.
- ✓ An agreement with the institution conducting this research was signed on Aug 29, 2022.
- ✓ Currently, we are recruiting research subjects.

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05. Part I. A Cohort-based Study on Long COVID-19

A Long COVID-19 Cohort

- ✓ A combined retrospective and prospective, longitudinal, observational cohort
- ✓ Subjects

Individuals including children, adolescents and adults with and without a history of COVID-19 infection will be enrolled in the cohort, and will be followed up to 3 years.

Infected:
9,000 individuals confirmed with COVID-19 at the time of the Delta or Omicron.
(visit every 6 months)
1,000 individuals with COVID-19 will be enrolled in the prospective sub-cohort.
(visit 1-2 week, 1-2 month, 3 month, 6 month, and then every 6 month)
In-patient sub-cohort will include at least 1% of the total # of the cohort.

Uninfected:
1,000 individuals without a history of COVID-19 infection will be the control group.

- ✓ Biological specimens will be collected in 10% of the each sub-cohorts.

Treatment Guideline

- ✓ Treatment guideline will be updated twice a year, including the latest research trends and research results of this project.

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05. Part II. A Big data-based Study on Long COVID-19

Integrated DB for long COVID-19

- ✓ Establish an integrated DB
  consisting of CDM-based longitudinal clinical data from Part I, multi-omics data from human specimens of Part III, and big data from public sectors (KCDC, health insurance, etc)
- ✓ Develop analysis methodology through standard DB construction
- ✓ Open the DB platform to public and Utilize it for public health

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05. Part III. A Translational Research on Long COVID-19

Research using patient samples from Part I and other derivative cohorts

- ✓ A derivative cohort and the subsequent validation cohort will be set up for respiratory symptoms, neurological symptoms, and other specific conditions of long COVID-19

  - will Investigate pathophysiology of long COVID-19 symptoms of respiratory system through research on inflammatory cytokines, persistent virus infection, T cell immune response, etc.
  - will investigate inflammatory cytokines, immune profiles, blood synapse protein, omics analysis.

- ✓ Through multi-omics research, such as transcriptomics, proteomics, radiomics, pathophysiological causes will be identified and the related immune factors will be discovered.

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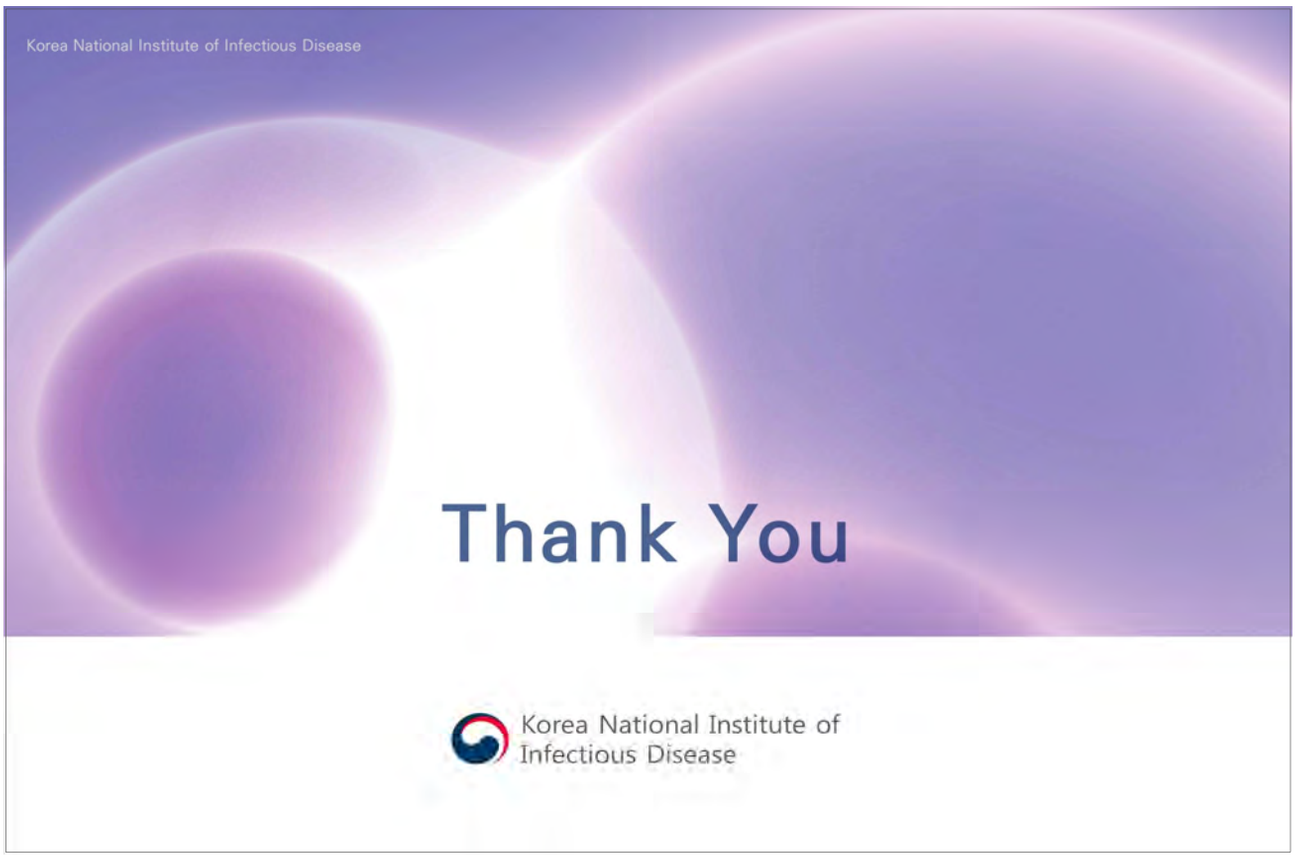

Korea National Institute of Infectious Disease
Thank You
Korea National Institute of
Infectious Disease

2. Long COVID treatment trials: pathogenesis guides intervention

Dr. David Lye (NCID, Singapore)

(Photo credit: National Centre for Infectious Diseases)

David LYE Chien Boon

1. Director,

Infectious Disease Research & Training Office, National Centre for Infectious Diseases (NCID)

2. Deputy Executive Director,

Programme for Research in Epidemic Preparedness and Response

3. Senior Consultant,

Department of Infectious Diseases, Tan Tock Seng Hospital

4. Professor,

Lee Kong Chian School of Medicine, NTU

- **EDUCATION:**

1996	MBBS, University of Melbourne, Australia
2004	Fellow, Royal Australasian College Physicians
2009	Fellow, Academy of Medicine, Singapore
2016	Fellow, Royal College of Physicians, Edinburgh

- **Research Interest**

Antimicrobial pharmacotherapy, stewardship and resistance; Dengue

- **PROFESSIONAL EXPERIENCE:**

2014 ~ current	A/Prof, Yong Loo Lin School of Medicine, NUS, Singapore
2016 ~ 2022	A/Prof, Lee Kong Chian School of Medicine, NTU, Singapore
2022 ~ current	Prof, Lee Kong Chian School of Medicine, NTU, Singapore
2021 ~ current	Adj Investigator, A*STAR Infectious Diseases Labs, A*STAR Research Entities
2018 ~ current	Director, Infectious Diseases Research and Training Office, NCID Singapore
2021 ~ current	Co-director, Respiratory and Infectious Diseases Research Programme, Lee Kong Chian School of Medicine, NTU, Singapore

2021 ~ current	Deputy executive director, Programme for Research in Epidemic, Preparedness and Response (PREPARE)

• SUMMARY

Topic: Long COVID treatment trials: pathogenesis guides intervention

Abstract

I will discuss principles underlying an immunologic approach to pandemic preparedness, progress made in designing serologic assays and widening our international partnerships, an EV-D68 pilot study, and specific projects to identify neutralizing antibodies against viruses including SFTSV and Langya virus

Part 1. One health & Infectious disease

Chair:
Yeon-sook Kim, M.D., PhD.

1. Serosurveillance and Immunogenicity Studies on COVID-19 in Korea
Dr. Byoung-guk Kim (NIID, Korea)

2. How to use and integrate whole genome sequencing into outbreak investigation programs – the example of CPO and VRE in Denmark
Dr. Ute Wolff Sönksen (SSI, Denmark)

Part 1. One health & Infectious disease

Moderator

Yeon-Sook Kim

Professor/Director of Daejeon Center for Infectious Diseases Control

Chungnam National University School of Medicine, Chungnam National University Hospital

- **EDUCATION:**

2005	Medicine (Degree of Doctor) Chungnam National University Graduate school
2001	Medicine (Degree of Master) Chungnam National University Graduate school
1996	Medicine Chungnam National University School of Medicine

- **PROFESSIONAL EXPERIENCE:**

2016 ~ Present	Professor Chungnam National University School of Medicine
2005 ~ 2022	Chief of Division of Infection Control Chungnam National University Hospital
2008 ~ 2016	Associate Professor Chungnam National University School of Medicine
2002 ~ 2008	Clinical Professor Chungnam National University School of Medicine

1. Serosurveillance and Immunogenicity Studies on COVID-19 in Korea

Dr. Byoung-guk Kim (NIID, Korea)

Byoung-guk Kim

Director

Division of Vaccine Clinical Research
Center for Vaccine Research (CVR)
National Institute of Infectious Disease (NIID)
National Institute of Health (NIH)

- **EDUCATION:**

1996 ~ 2004	Doctor (Ph.D.) Department of Biology (major field: Virology) Kyung Hee University, Seoul, Republic of Korea
1994 ~ 1996	Master of Science (MS) Department of Biology (major field: Microbiology) Kyung Hee University, Seoul, Republic of Korea

- **PROFESSIONAL EXPERIENCE:**

2020 ~ Present	Director Division of Vaccine Clinical Research Center for Vaccine Research (CVR) National Institute of Infectious Disease (NIID)
2017 ~ 2019	Technical Specialist Pan American Health Organization/World Health Organization(PAHO /WHO)
1997 ~ 2017	Ministry of Food and Drug Safety Dr. Kim carried out researches on the development and standardization of testing methods for the clinical efficacy evaluation of vaccines, and national standard materials. He had been striving to improve the quality of biopharmaceuticals including vaccines for more than twenty years as a Regulatory Affairs and Quality Assurance Specialist.
2009 ~ 2012	Scientific Officer, Ministry of Food and Drug Safety

• SUMMARY

Topic: Serosurveillance and Immunogenicity Studies on COVID-19 in Korea

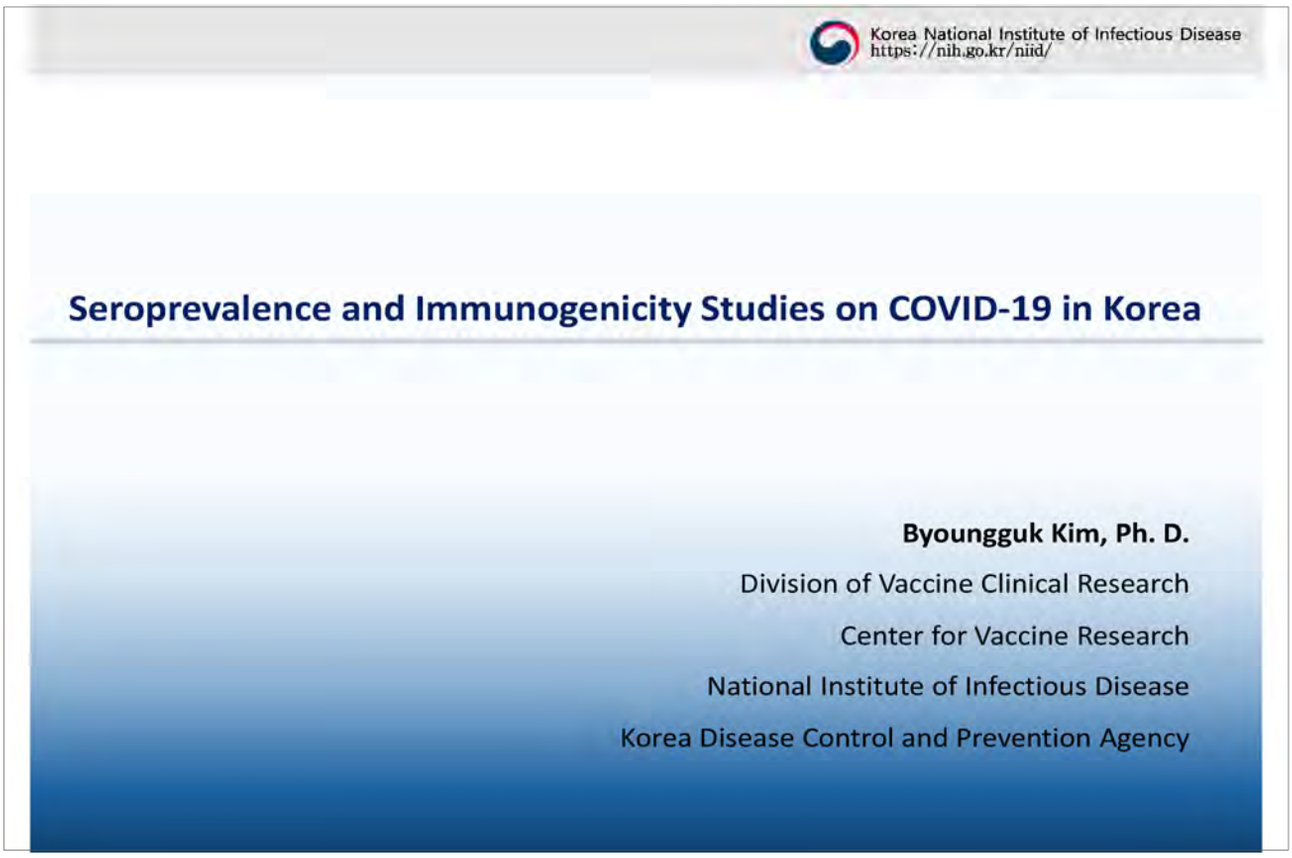
Abstract

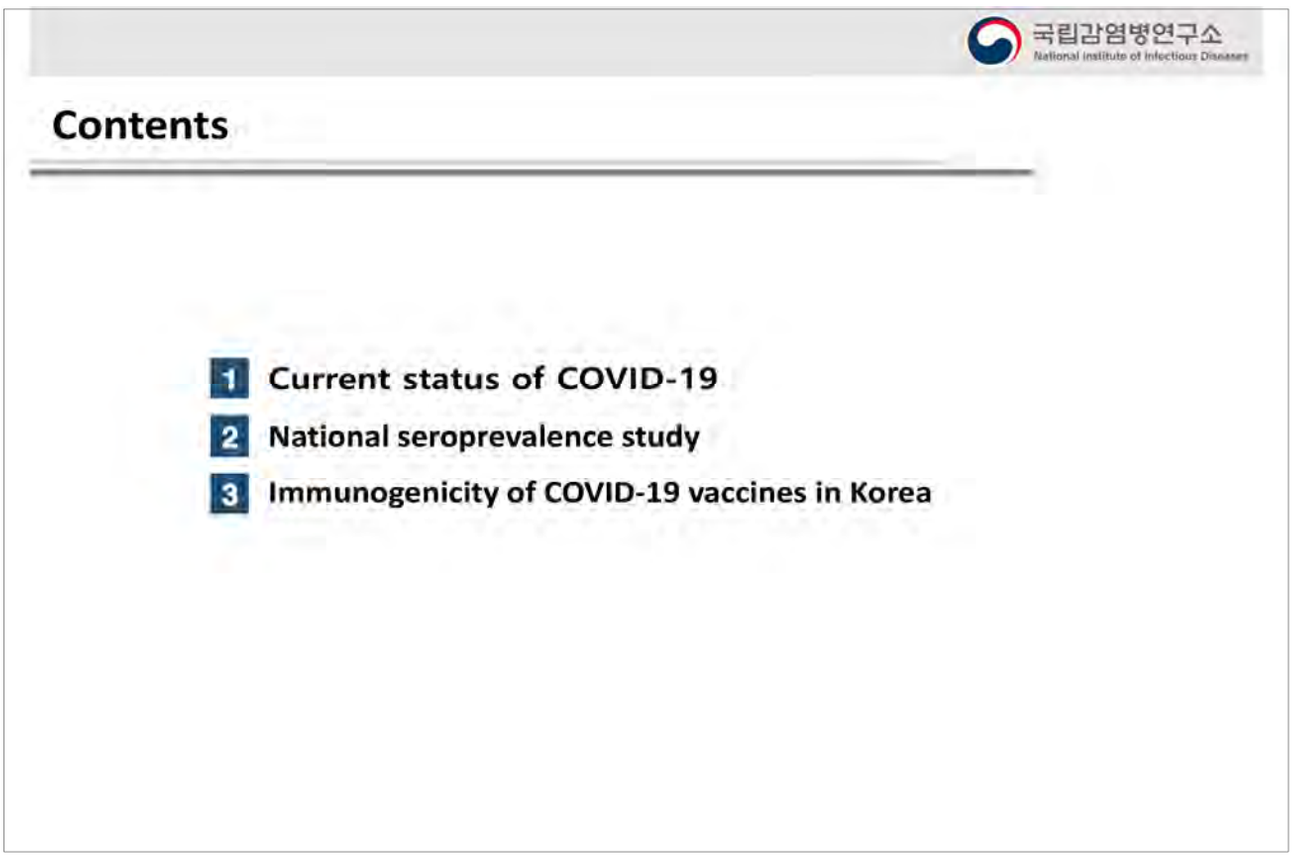
The division of vaccine clinical research, NIID is conducting national immunity survey and immunogenicity studies of COVID-19 vaccine recipients.

The antibody positive rate survey can estimate the level of antibodies acquired by vaccination and infection. National representative samples were selected from 17 provinces for analysis of seropositivity. The immunity level was confirmed using by antibody binding assay for SARS-CoV-2 spike protein and nucleocapsid protein. In the first survey, anti-S positivity of 9,945 subjects was 97.6%, and anti-N positivity was 57.2% in August 2022. In the second survey progressed in December 2022, the anti-S positivity of 7,528 subjects was maintained as 98.6%, and the anti-N positivity showed 70.0% by increasing 12.8% after the first survey.

COVID-19 vaccine s had been rapidly developed and were introduced in Korean society in early 2021. In this study, we aimed to investigate the short-term and long-term immunogenicity of diverse COVID-19 vaccine platforms after primary series and booster vaccination in healthy adults aged 20-59 years. Primary vaccination series elicited neutralizing against SARS-CoV-2 wild-type (WT) in all participants and the antibodies titers reached peak 2-4 weeks after the second dose. However, the vaccine effectiveness waned over time and resistance to vaccine-immunity of variants of concern increased. From late 2021, individuals were encouraged to receive a 3rd dose to overcome the immune escape of Delta and Omicron. The booster shot induced strengthened not only neutralizing antibodies against WT but those against Delta and Omicron variants.

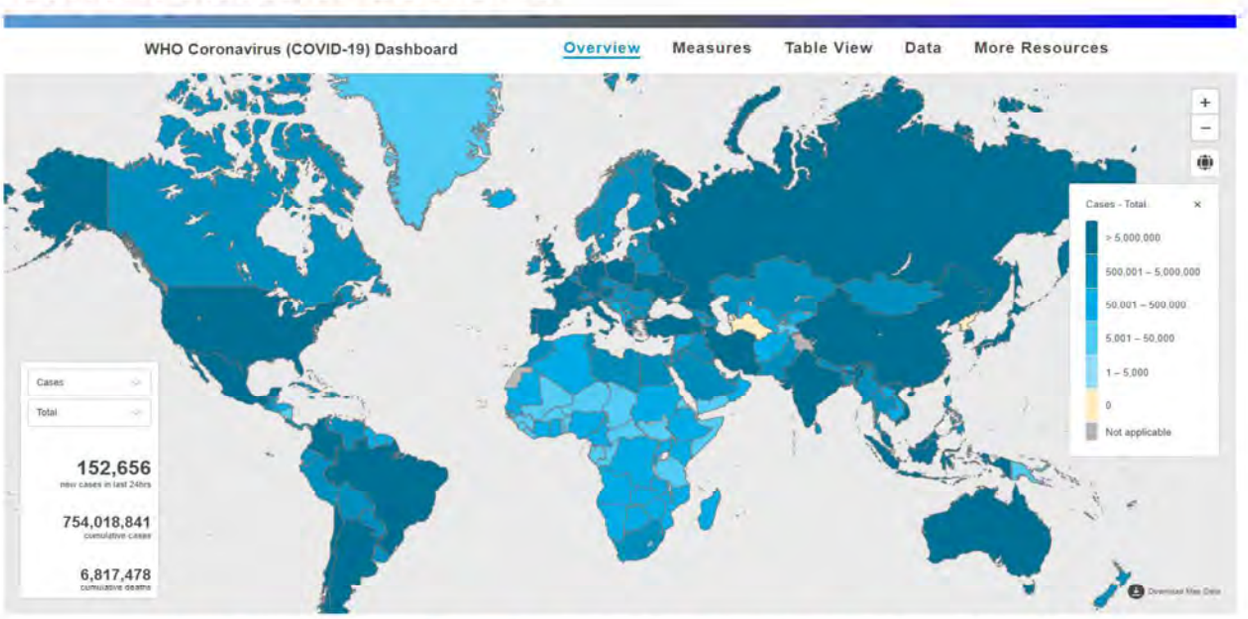
To establish public health strategies against emerging SARS-CoV-2 variants, it is planned to continuously present laboratory-based evidence by conducting the antibody positivity survey, and long-term follow-up studies on immune response and antibody persistence after vaccination.


Korea National Institute of Infectious Disease
https://nih.go.kr/niid/
Seroprevalence and Immunogenicity Studies on COVID-19 in Korea
Byoungguk Kim, Ph. D.
Division of Vaccine Clinical Research
Center for Vaccine Research
National Institute of Infectious Disease
Korea Disease Control and Prevention Agency


국립감염병연구소
National Institute of Infectious Diseases
Contents
1 Current status of COVID-19
2 National seroprevalence study
3 Immunogenicity of COVID-19 vaccines in Korea

1 Current status of COVID-19

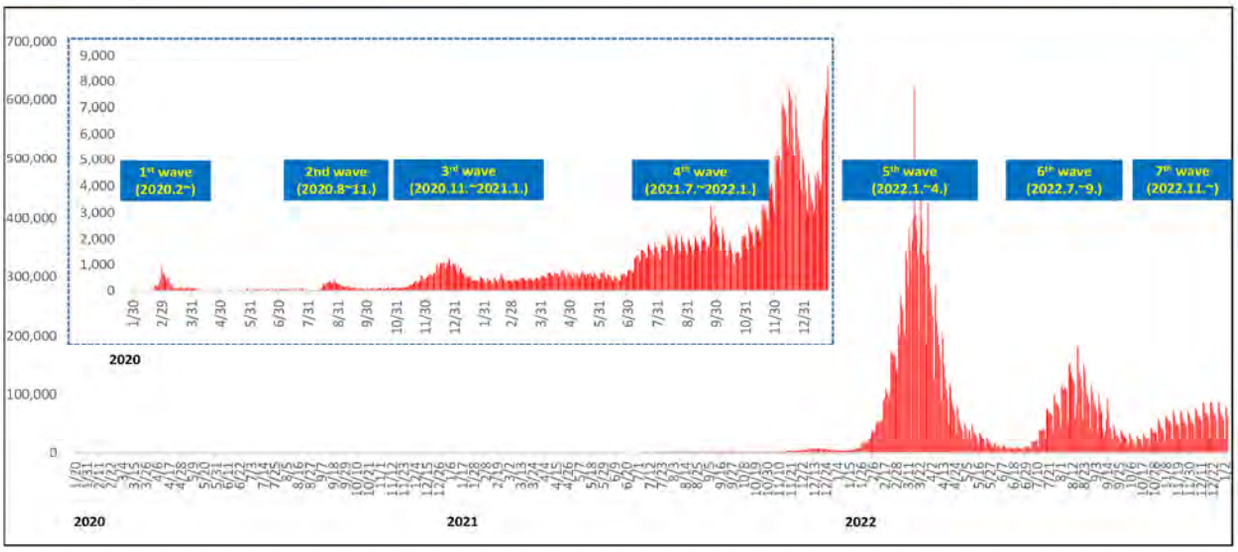
Current status of COVID-19



Globally, as of 6:14pm CET, 3 February 2023, there have been 754,018,841 confirmed cases of COVID-19, including 6,817,478 deaths, reported to WHO. As of 30 January 2023, a total of 13,168,935,724 vaccine doses

WHO, https://covid19.who.int/

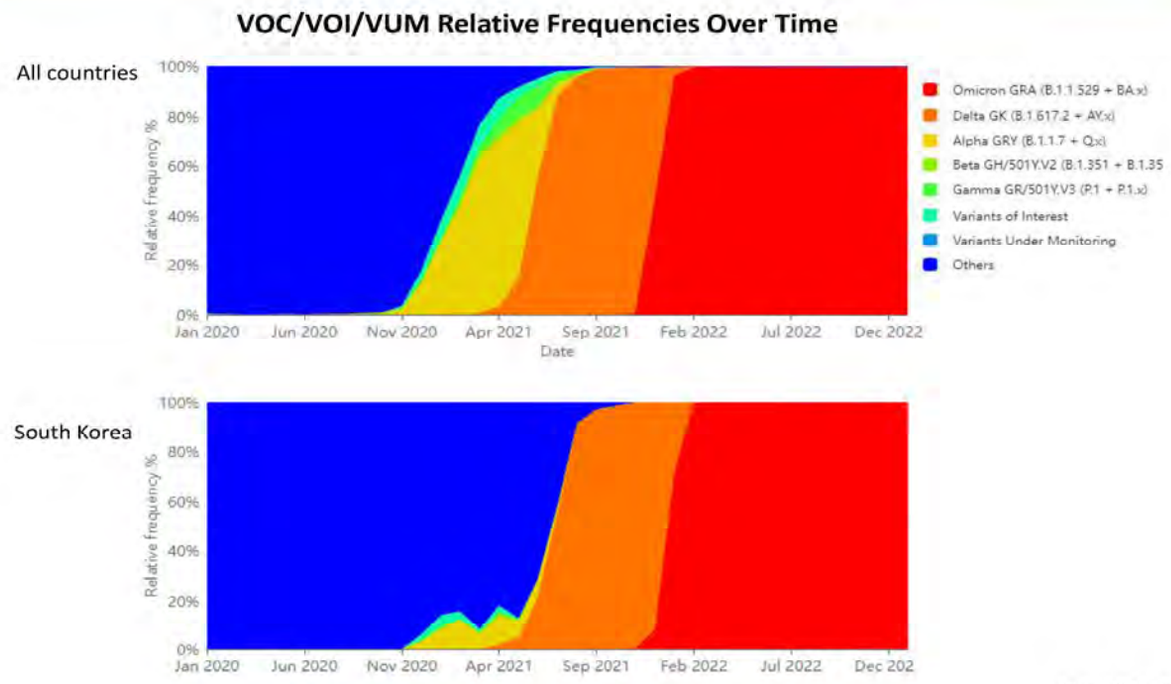
SARS-CoV-2 outbreak in Rep. of Korea



Daily confirmed cases of COVID-19 since January 20, 2020

https://ncov.kdca.go.kr/

Variation of concern

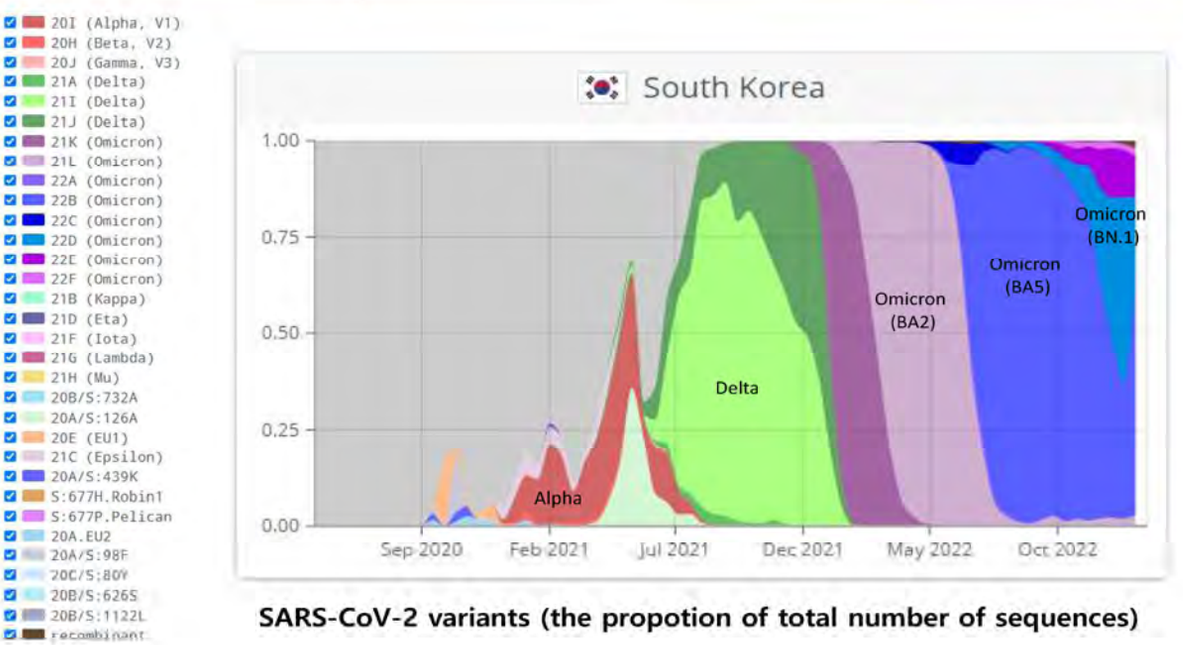


https://gisaid.org/

Variation of concern

WHO label	Pango lineage	Earliest documented samples
Alpha	B.1.1.7	United Kingdom, Sep-2020
Beta	B1.351	South Africa, May-2020
Gamma	P.1	Brazil, Nov-2020
Delta	B.1.617.2	India, Oct-2020
Omicron	B.1.1.529	Multiple Countries, Nov-2021

Overview of Variants in Rep. of Korea



SARS-CoV-2 variants (the propotion of total number of sequences)

CoVariants.org

COVID-19 vaccination in Rep. of Korea

Vaccination introduction date in Rep. of Korea

Feb-2021. first vaccination
- ChAdOx1 nCOV-19 (Astrazeneca)
- BNT162b2 (Pfizer)
- heterologous vaccination(AZ and Pf)
- mRNA-1273 (Moderna)
- Ad.26.COV2.S (Janssen)

Oct-2021. third vaccination
- BNT162b2 (Pfizer)
- mRNA-1273 (Moderna)

Feb-2022. Forth vaccination for high risk group
- BNT162b2 (Pfizer)
- mRNA-1273 (Moderna)

Nov-2022. bivalent vaccination
- BA.1, BA.4/5 (Pfizer)
- BA.1 (Moderna)

Classification	2nd vaccination rate(%)
> 60 years old	96.6
> 18 years old	96.7
> 12 years old	94.2

(2023.2.6.)

WHO, Tracking SARS-CoV-2 variants
Korea Disease Control and Prevention Agency(2023.2.6)

2 National seroprevalence study

Seroprevalence studies of COVID-19

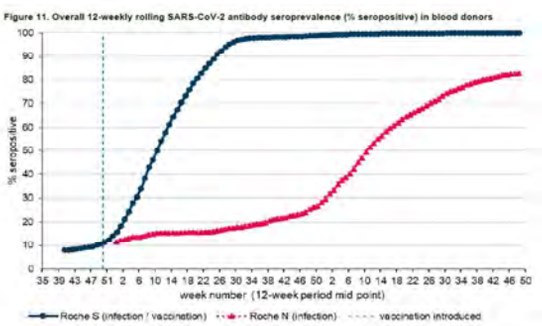
To estimate the level of antibodies acquired by vaccination and/or infection in national representative samples

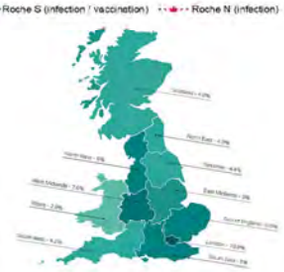
Estimated seroprevalence studies of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in different countries
→ 3,924 seroprevalence studies In 140 countries and territories Including 32,936,516 participants

serotracker

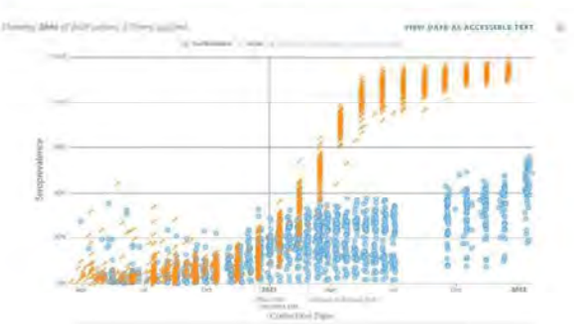
Seroprevalence studies of COVID-19

UK: 14,500 blood donors of 17 years old, Roche N/S
(COVID-19 vaccine surveillance report, UK Health Security Agency, Jan. 2023)





US: unit states investigation, Roche N/S, ELISA
(COVID-19 SeroHub, NIH & CDC, USA, Mar 1, 2022)



National seroprevalence study in Korea

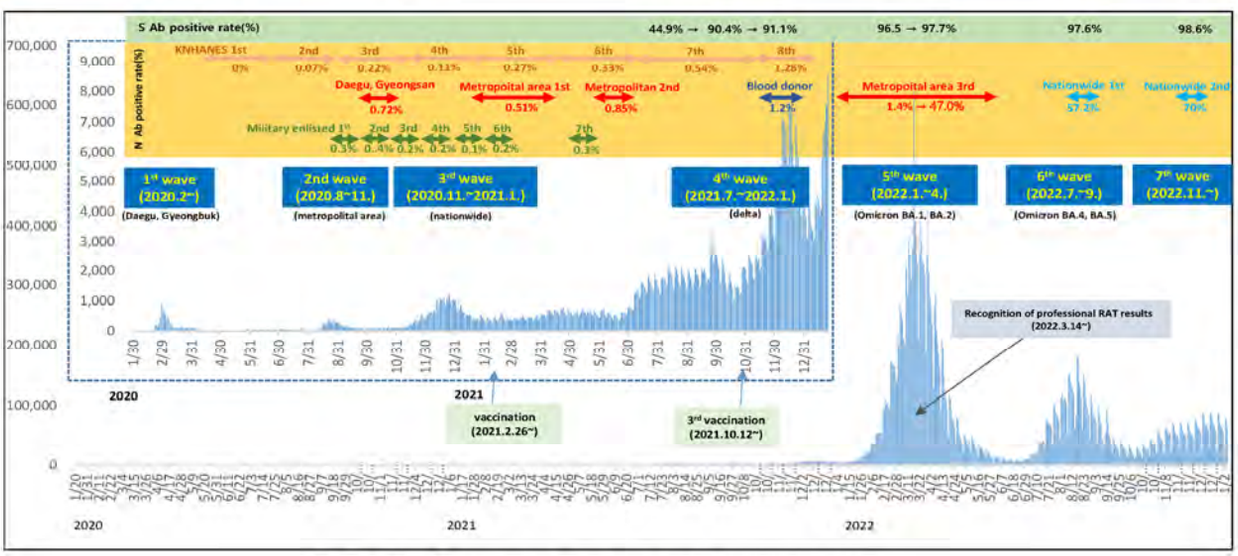
Purpose

Securing grounds for establishing quarantine measures and vaccination policies by identifying the exact scale of infection in the community, including unconfirmed infections in the community

Target populations

- Daegu, Gyeongsan, Metropolitan area
- National Health and Nutrition Examination Survey(KNHANES)
- Blood donors based on blood donation
- Military enlisted
- Periodic survey of a representative sample of 10,000 people (aged 5 years and older) in 17 provinces in nationwide

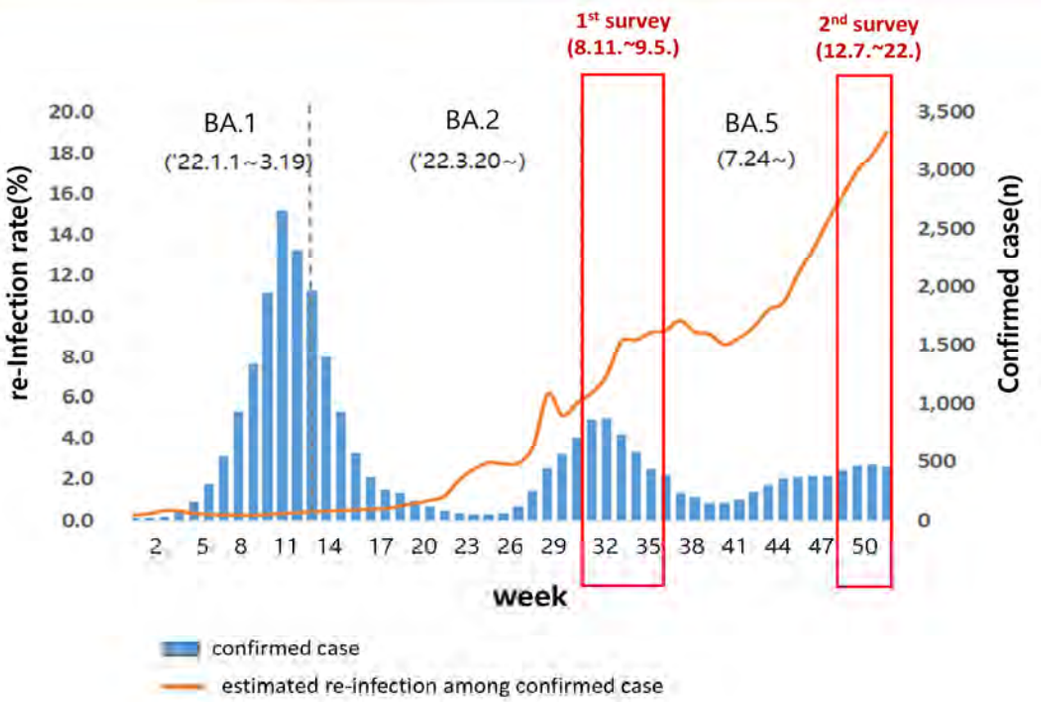
Result



SARS-CoV-2 outbreak and national seropositivity

- Roche antibody assays (CLIA, Binding Ab assay)
* N (nucleoprotein) : antibody after natural infection
** S (spike) : antibody after infection and induced by vaccination

Period of Nationwide antibody survey



Result

1st survey

- Total research period : July 1, 2022 ~ October 31, 2022
  - Blood sampling period : August 11, 2022 ~ September 5, 2022
- Number of participants : total 9,945
- Test method : antibody test against S and N antigen of SARS-CoV-2

1. antibody positive rate due to **natural infection : 57.2**

- cumulative incidence rate of confirmed cases : 37.8% (as of July 31, 22)

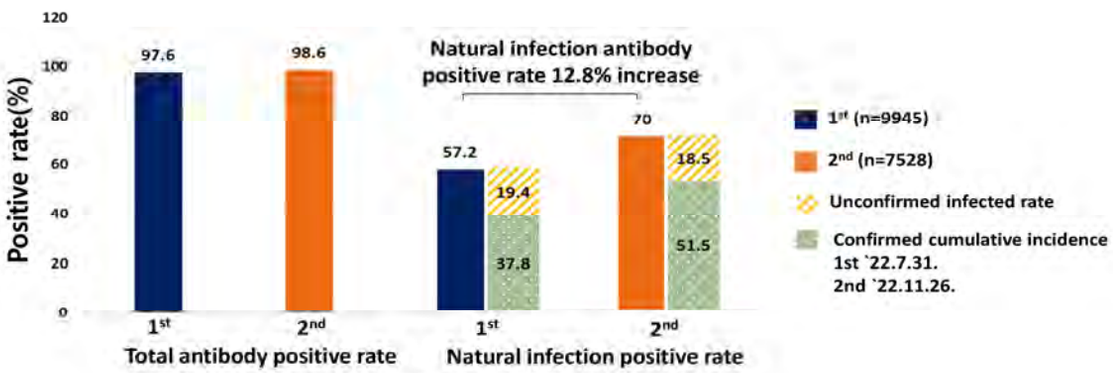
→ 19.4% difference compared to the cumulative incidence of confirmed cases

2. **Total antibody positive rate (natural infection + vaccination) : 97.6%**

Result

2nd survey

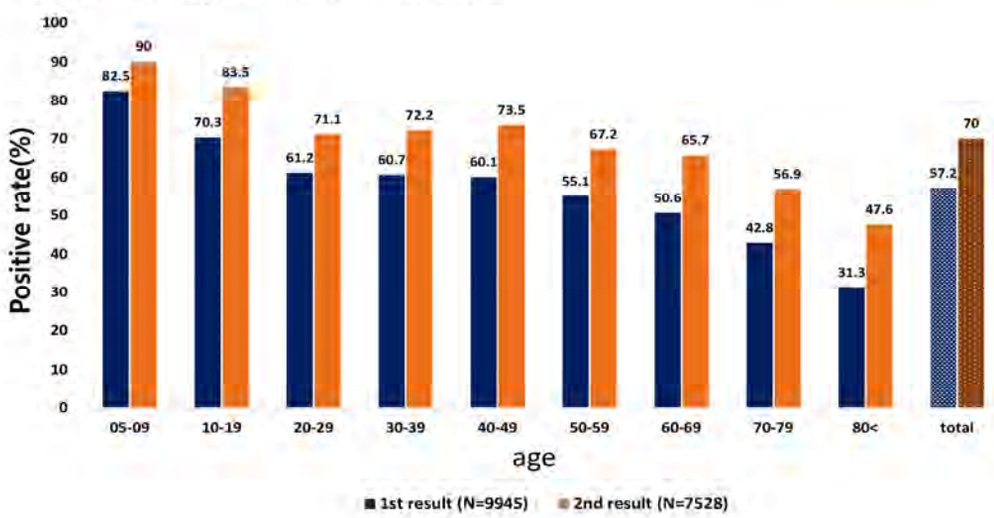
- Blood collection period : December 7, 2022 ~ December 22, 2022
- Number of participants : 7,528 (75.7%) of the 9,945 participants in the 1st survey who wish to participate in the 2nd survey
- Test method : antibody test against COVID-19 S and N antigen



- ✓ Total antibody positive rate (S+N) : 98.6%
- ✓ Natural infection antibody positive rate(N) : 70.0%
- ✓ Unconfirmed infection rate : 18.5%

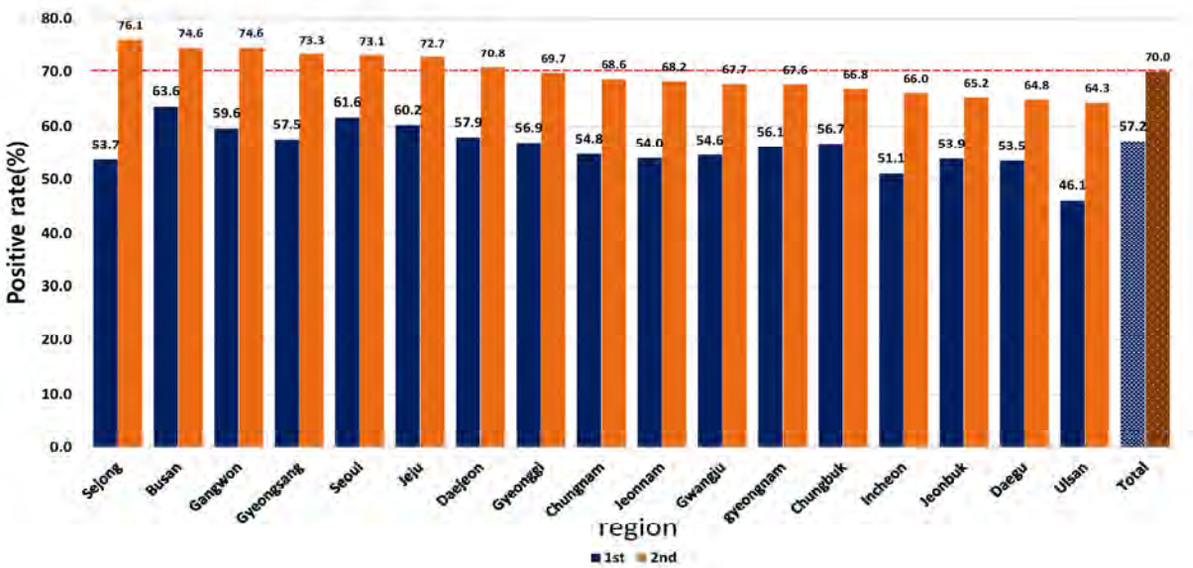
Result

N antibody positive rate by age



Result

N antibody positive rate by region

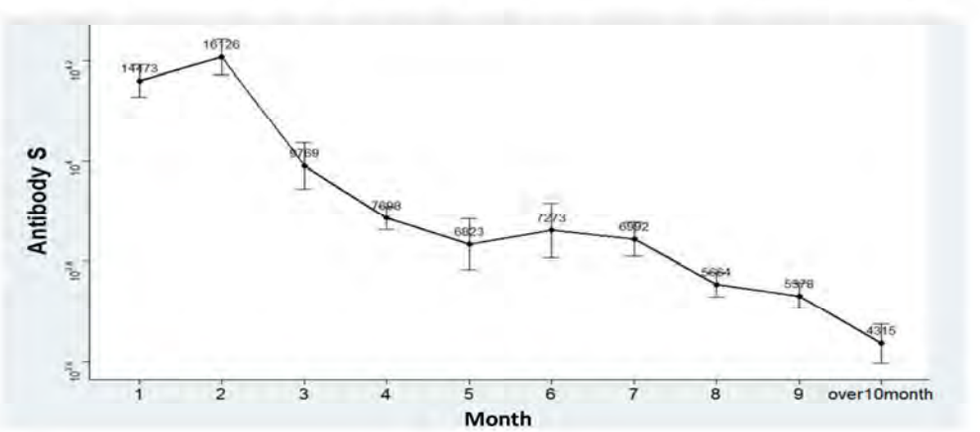


Result

Antibody titer decrease by Period

- Antibody titer decrease by period of 9,006 participants who were vaccinated and/or confirmed before blood collection

→ Antibodies decrease from 3 months after vaccination and confirmation



Result

Relative risk according to the antibody titer

Analysis of infection status for 6,769 people who did not receive additional vaccination after the 1st survey

→ As a result of quartile (Q1~Q4) analysis,

the lower the titer level, the higher the risk of infection

	Titer	Case number	Confirmed case	Incidence rate(%)	Relative Risk (CI)
Q1 (under Q25)	~1545	1693	222	13.1	7.9(4.9-12.9)
Q2 (Q25-50)	1545-5942	1693	95	5.6	3.7(2.3-5.9)
Q3 (Q50-75)	5942-16111	1691	23	1.4	1.3(0.9-2.0)
Q4 (Q75-100)	16111~	1692	15	0.9	Ref.
Total	-	6,769	355	5.2	-

3 Immunogenicity of COVID-19 vaccines in Korea

Project Overview

Purpose

To compare neutralizing activities against Omicron and Delta variants after three-dose vaccination schedules

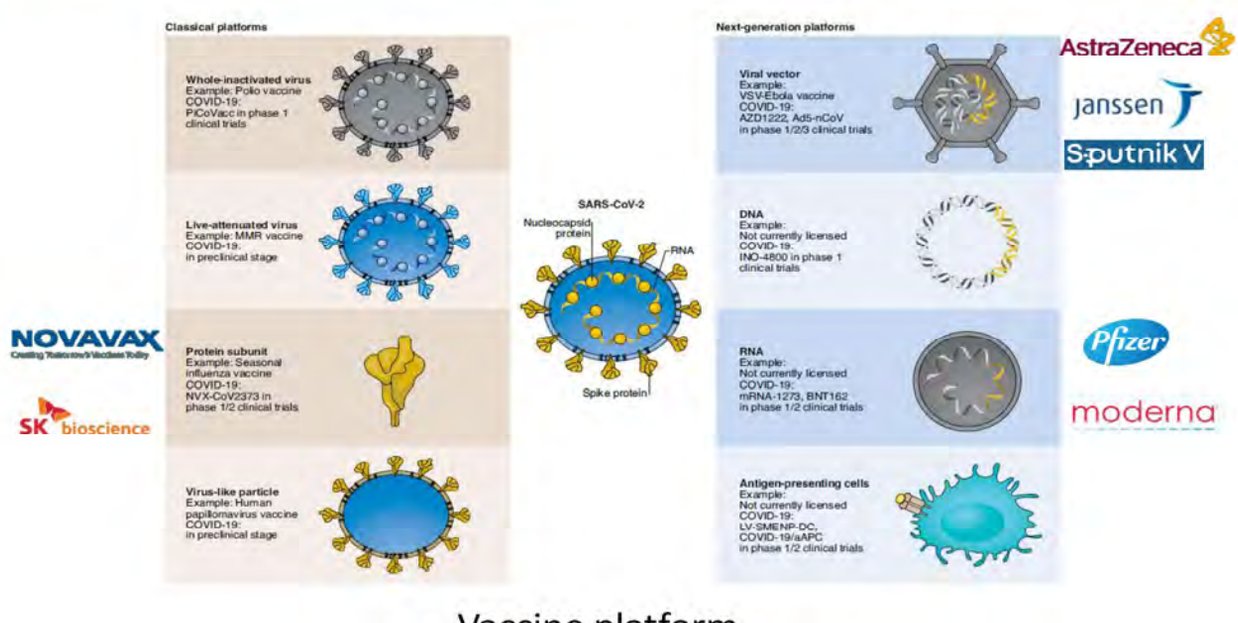
Vaccination Group for Analysis

- ✓ BNT162b2 (Pfizer/BioNTech)
- ✓ ChAdOx1 (AstraZeneca)
- ✓ Heterologous AstraZeneca and Pfizer
- ✓ mRNA-1273 (Moderna)
- ✓ NVX-CoV2373 (Nobavax)

Method for analysis

PRNT against wild type (WT), Delta variant, and Omicron variant of severe acute respiratory syndrome virus 2 (SARS-CoV-2)

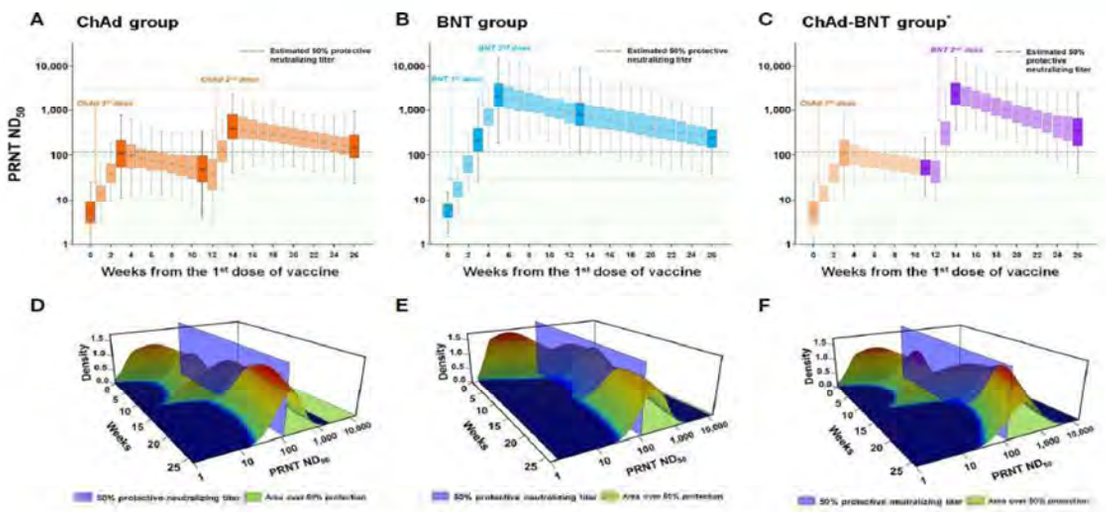
Background



Vaccine platform

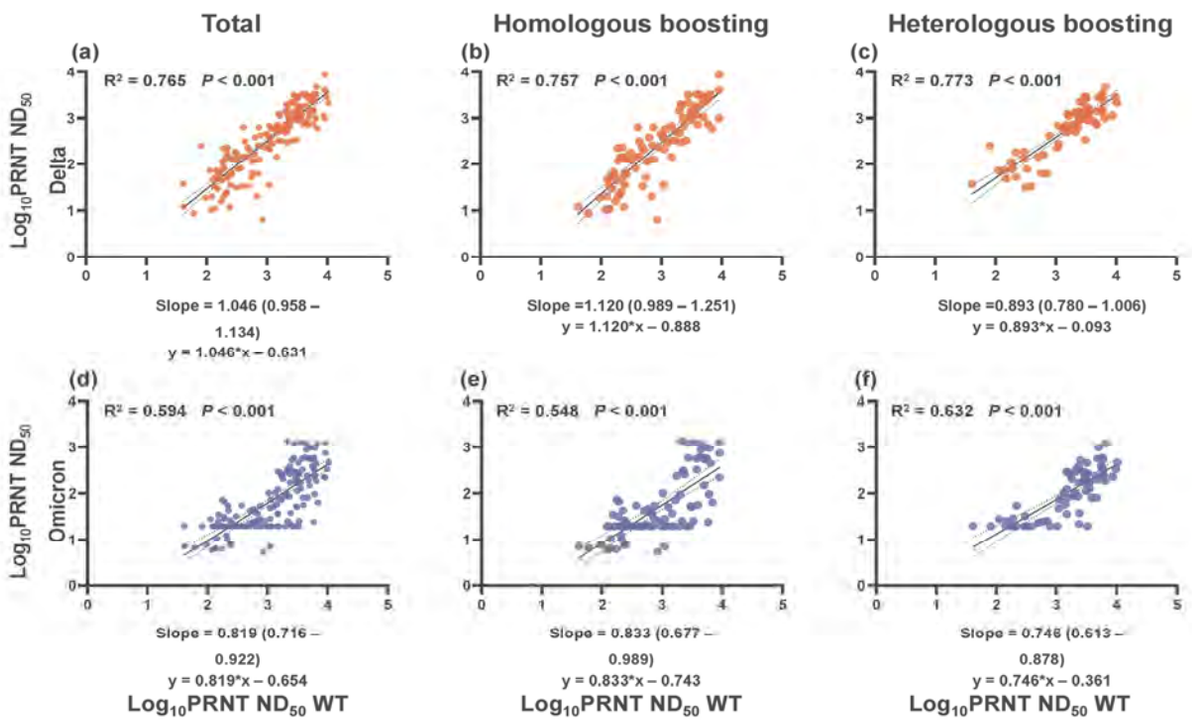
Nature Materials 19:810(2020)

Result



Kinetics of Vaccine-induced neutralizing antibody
: nationwide cohort study comparing 3 vaccination

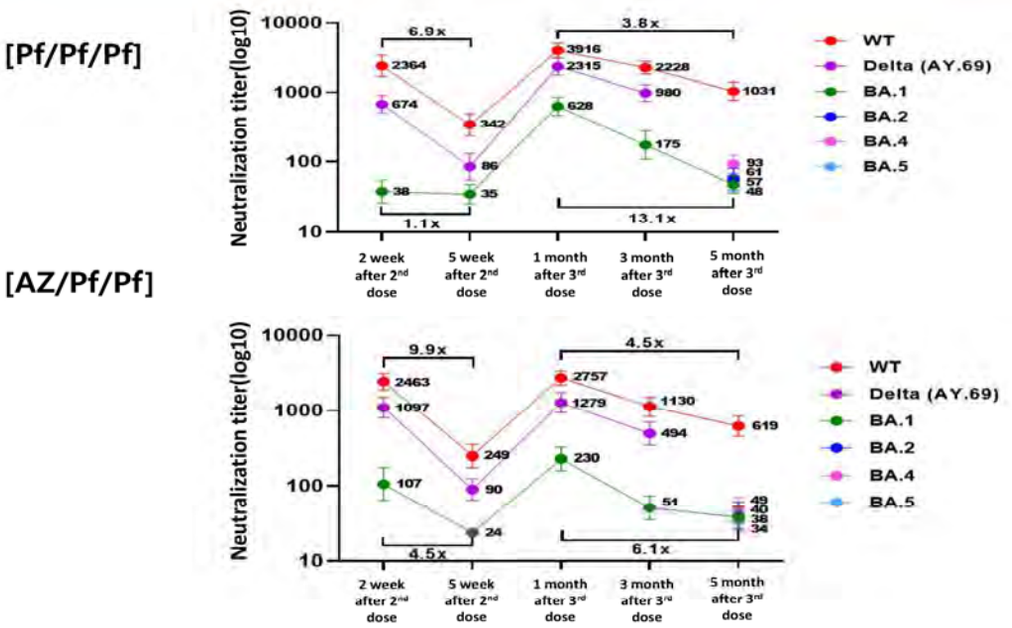
Eliel Nham et al. 2022



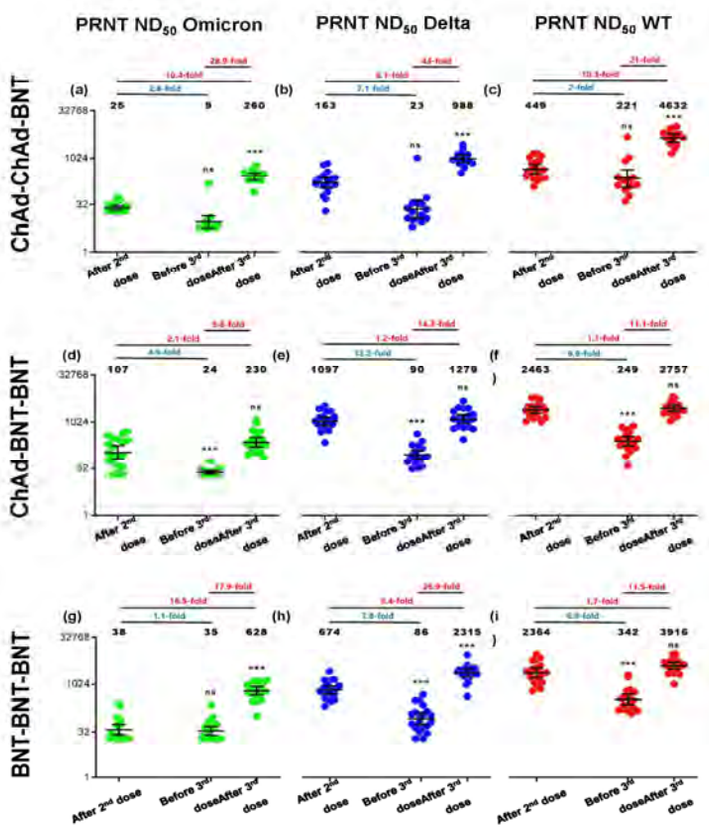
PRNTND50 correlation between WT and Delta or Omicron variant

Ju-yeon Choi et al., 2022

Result

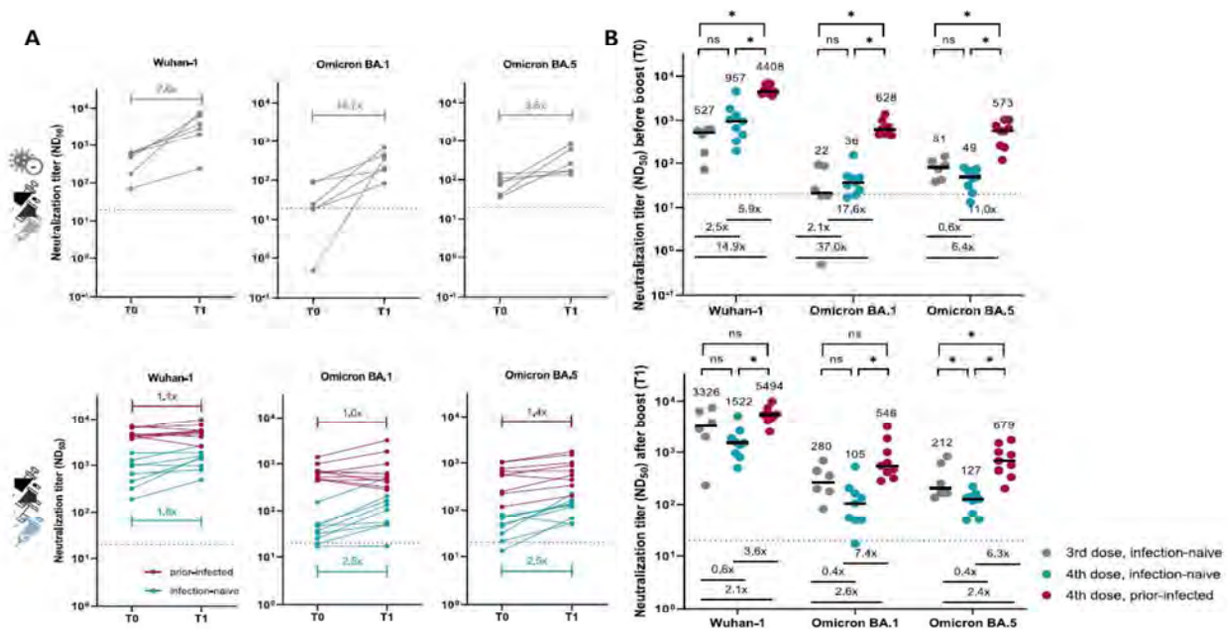


Duration of maintain neutralizing antibodies against Delta and Omicron



PRNT ND50 against Delta and Omicron variants compared to Wild-type SARS-CoV-2 for each vaccination schedule.

Ju-yeon Choi et al., 2022



Neutralization titers against wild-type Wuhan-1 strain and Omicron subvariants BA.1 and BA.5 in individuals who received the third or fourth dose vaccination with NVX-CoV2373

M.J. Choi, J.-Y. Choi, H. Hyun et al., 2022

Thank You
National Institute of Health

2. How to use and integrate whole genome sequencing into outbreak investigation programs – the example of CPO and VRE in Denmark

Dr. Ute Wolff Sönksen (SSI, Denmark)

Ute Wolff Sönksen

Senior Medical Officer

Reference Laboratory of Antibiotic Resistance

Statens Serum Institut, Denmark

- **EDUCATION:**

1991 ~ 2001	Medical Doctor, University of Southern Denmark
2007 ~ 2012	Specialist training in Clinical Microbiology

- **PROFESSIONAL EXPERIENCE:**

2020 ~ 2021	Technical Officer at AMR unit, WHO Europe
2015 ~ present	Senior Physician at Reference Laboratory of Antimicrobial Resistance, Statens Serum Institut, with related academic and professional positions:

2021 ~ present: chair of AMR group at Statens Serum Institut

2015 ~ present: member of the National Antibiotic Council, Denmark

2016 ~ present: Head of AMR surveillance programme and member of the DANMAP steering group, Denmark

2016 ~ present: member of the AMR/One Health expert group of the Nordic countries (under the Nordic council of ministers)

2016 ~ present: Danish focal point for antimicrobial resistance and antimicrobial consumption, ECDC

2016 ~ present: member of the working group for use of antibiotics, the Danish medicine council

2013 ~ present: member of the DANRES group, a method group for antimicrobial resistance testing under the Danish Association of Clinical Microbiology

2014 ~ present: member of the ESCMID ESGAP group.

2022: Danish member of the EU One Health AMR expert group

- **PROFESSIONAL EXPERIENCE:**

2015	Department of Clinical microbiology, Odense University Hospital, Odense
2013 ~ 2014	Department of Clinical Microbiology at Sydvestjysk sygehus, Esbjerg.
2008 ~ 2012	Clinical training and specialization in Clinical Microbiology, Capitol region of Denmark
2007 ~ 2008	Internship at department of children's and adolescent psychiatry, Glostrup Hospital
2005 ~ 2007	Internship at Department of Clinical Microbiology, Hillerød Hospital
2003 ~ 2005	Internship at Department of pediatrics, Hillerød Hospital
2001 ~ 2003	Combined internship, internal medicine, abdominal surgery and general medicine, Frederiksborg Counsel, Capital region of Denmark

Part 2. Tuberculosis Vaccines

Chair:
Jae-joon Yim, M.D., PhD.

1. Development of the novel Tuberculosis vaccine applied to various platforms in Korea

Dr. Hye-Sook Jeong (NIID, Korea)

2. Overview of TB vaccine development

Dr. Rasmus Mortensen (SSI, Denmark)

Part 2. Tuberculosis Vaccines

Moderator

Jae-Joon Yim

Professor

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine

Seoul National University College of Medicine

- **EDUCATION:**

2007 ~ 2009	Mailman's School of Public Health, Columbia University, NY, USA M.S. – Patient Oriented Research
2000 ~ 2004	Seoul National University, Seoul, Republic of Korea Ph.D.
1997 ~ 1999	Seoul National University, Seoul, Republic of Korea M.S.
1990 ~ 1994	Seoul National University, Seoul, Republic of Korea M.D.,*Cum Laude*
1988 ~ 1990	Seoul National University, Seoul, Republic of Korea Premed. Program

- **PROFESSIONAL EXPERIENCE:**

2012 ~ Present	Professor, Division of Pulmonary and Critical Medicine Department of Internal Medicine Seoul National University College of Medicine / Seoul National University Hospital
2006 ~ Present	Associate Professor Division of Pulmonary and Critical Medicine Department of Internal Medicine Seoul National University College of Medicine / Seoul National University Hospital
2002 ~ present	Assistant Professor

- **PROFESSIONAL EXPERIENCE:**

	Division of Pulmonary and Critical Medicine Department of Internal Medicine Seoul National University College of Medicine / Seoul National University Hospital
2001 ~ 2002	Visiting Fellow Immunopathogenesis Unit Clinical Pathophysiology Section Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health U.S.A
2020 ~ 2001	Clinical Fellow Division of Pulmonary and Critical Medicine Department of Internal Medicine Seoul National University Hospital
1999 ~ 2000	Research Doctor Department of Internal Medicine and Lung Institute Seoul National University Hospital, Seoul, Korea
1994 ~ 1999	Internship and Residency in Internal Medicine Seoul National University Hospital, Seoul, Korea

Part 2
Tuberculosis Vaccines

1. Development of the novel Tuberculosis vaccine applied to various platforms in Korea

Dr. Hye-Sook Jeong (NIID, Korea)

Hye-Sook Jeong

Senior Staff Scientist

Division of Infectious Disease Vaccine Research, National Institute of Infectious Disease, NIH, KDCA

- **EDUCATION:**

2001 ~ 2004	Ph.D., chonnam National University
1999 ~ 2001	M. S, chonnam National University
1994 ~ 1998	B. S, Chosun university

- **PROFESSIONAL EXPERIENCE:**

2020 ~ Present	Senior Staff Scientist, Division of Infectious Disease Vaccine Research
2012 ~ 2020	Staff scientist, Division of Vaccine Research, KCDC
2006 ~ 2012	Staff scientist, Division of Enteric and Hepatitis Viruses, KCDC
2004 ~ 2005	Post Doc., Food Science and Technology, Seoul National University

- **SUMMARY**

Topic: **Development of the novel Tuberculosis vaccine applied to various platforms in Korea**

Abstract

Tuberculosis (TB) is the second leading infectious cause of mortality worldwide, with about two million deaths yearly. Globally in 2020, an estimated 5.8 million incident cases were caused by M. tuberculosis. Moreover, there are an estimated 1.3 million deaths from TB. South Korea ranked the highest TB incidence among the Organization for Economic Cooperation and Development (OECD) members. The only licensed vaccine, Mycobacterium bovis Bacillus Calmette Guerin (BCG), is effective in infants and adolescents. Unfortunately, the varying immune efficacy and short duration cause limited protection effects, so the BCG vaccine does not protect all generation groups from tuberculosis. Although significant progress in the search for a more effective TB vaccine has been demonstrated over the last two decades, there is still no replacement for the licensed BCG vaccine. Since 2018,

the Korean government has implemented the “Midterm strategies to strengthen TB prevention and management” based on the 2nd National Strategic Plan for Tuberculosis Control (2018-2022). The program includes a strategy to support the development of a new tuberculosis vaccine. In this session, we would like to introduce the developing status of the new tuberculosis vaccine using various platforms and new formulation, in Korea.

질병관리청
국립감염병연구소

23, February, 2023

Development of the novel Tuberculosis vaccine applied to various platforms in Korea

Jeong, Hye-Sook, Ph.D.
Division of Infectious Disease Vaccine Research, NIID, KNIH

1st IDRIC
International Symposium for Infectious Diseases Research Institutes Cooperation

Contents

1 Background
2 TB vaccine pipeline in Korea
3 The study of viral vectored TB vaccine
4 Novel platform application
5 summary

TB REMAINS A LEADING CAUSE OF DEATH

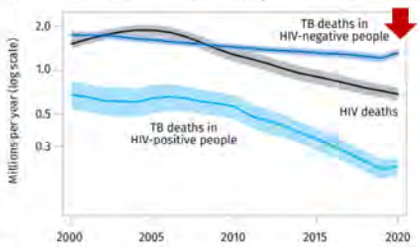
 # 1 Killer due to a single pathogen except for SARS-CoV-2

- **IN 2020, 10 million new cases of TB and 1.5 million deaths**
  - **8-9% of TB cases and ~14% of TB deaths are in over Persons Living with HIV**

- **COVID-19 had substantial impact**
  - **Reduced access to diagnostic, treatment and preventive services**
  - **TB deaths increased for the first time in over a decade**
  - **Reduction in incidence halted**
  - **Impacts predicted to be even worse in 2021 and 2022**

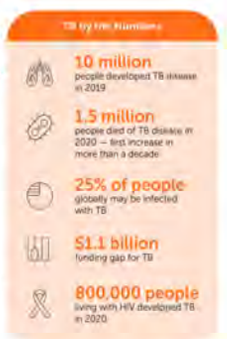
Global trends in the estimated number of deaths caused by TB and HIV, 2000–2020[a,b]

Shaded areas represent uncertainty intervals.



[a] For HIV/AIDS, the latest estimates of the number of deaths in 2020 that have been published by UNAIDS are available at http://www.unaids.org/en/. For TB, the estimates for 2020 are those published in this report.

[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.



Global tuberculosis report, 2021

Current situation of TB in Korea

- **No. of New cases : 35.7 cases per 100,000 persons (2021)**
- **No. of TB Deaths : 2.6 cases per 100,000 patients (2020)**
- **Among OECD (37 countries), South Korea was the highest TB incidence and ranked 3rd in TB mortality (2021)**

TB incidence in Korea, 2001-2021

TB mortality in Korea, 2001-2020

The END TB Strategy (2015-2030)

- Establishment of the Sustainable Development Goals (SDGs)
  - → **Prepare a more robust strategy to eradicate tuberculosis**
- Requires policy efforts to achieve the goal of eradicating tuberculosis by 2030
- Infrastructure maintenance and management
  - → (Strategy) ① Patient-centered integrated tuberculosis management and prevention, ② Bold policies and support systems, ③ Strengthening research and innovation activities

Indicators	WHO End TB strategy (2015-2030)	1st Goal (2015-2020)	1st Status (2015-2020)	
			Global	South Korea
TB Incidence (%)	80 % reduction	20 % reduction	11.0 % reduction	38.0 % reduction
No. TB Death	90 % reduction	35 % reduction	9.2 % reduction	25.9 % reduction

The 2nd National Strategic Plan for TB control (2018-2022)

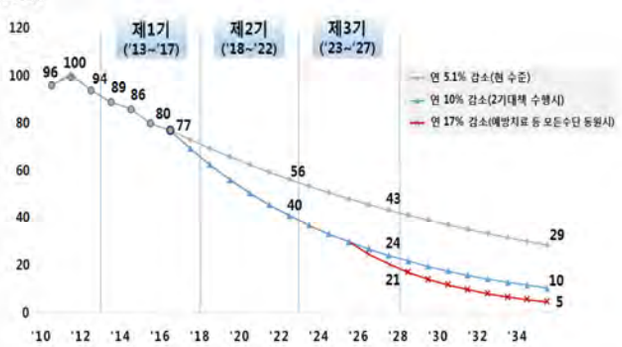
Vision TB free Society, Healthy Country

Goal 50% reduction in TB Incidence by 2022 (compared to 2016)

* 77 people in 2016 → 40 people in 2022 (per 100,000)

Strategy

① Early detection of TB patients
② Comprehensive TB patients management
③ Strengthening R&D
④ Enhancement of the infrastructure



BCG is the only licensed TB vaccines – in use since 1921

100-year-old BCG vaccine is the most widely used vaccine in the world BUT...

Lessons from BCG vaccines

- **Safe** : more than 1 billion doses
  ~80% of children in the world
- **Inexpensive**

Wide variation in protective efficacy **(0~80%)**
- Prevent meningitis and military TB in children with average protection of **~ 80%**
- Not able to prevent *M.tb* infection in child

➢ **Widespread use of infant BCG has not effectively protected adolescents and adults from developing active TB disease**

Strategy to developing Novel TB vaccines

Infants & neonates	Prevention-of-infection vaccine (POI)
Adolescents & Adults	Prevention-of-disease vaccine (POD)
Therapeutic	Prevention-of-recurrence (POR) or Therapeutic vaccine

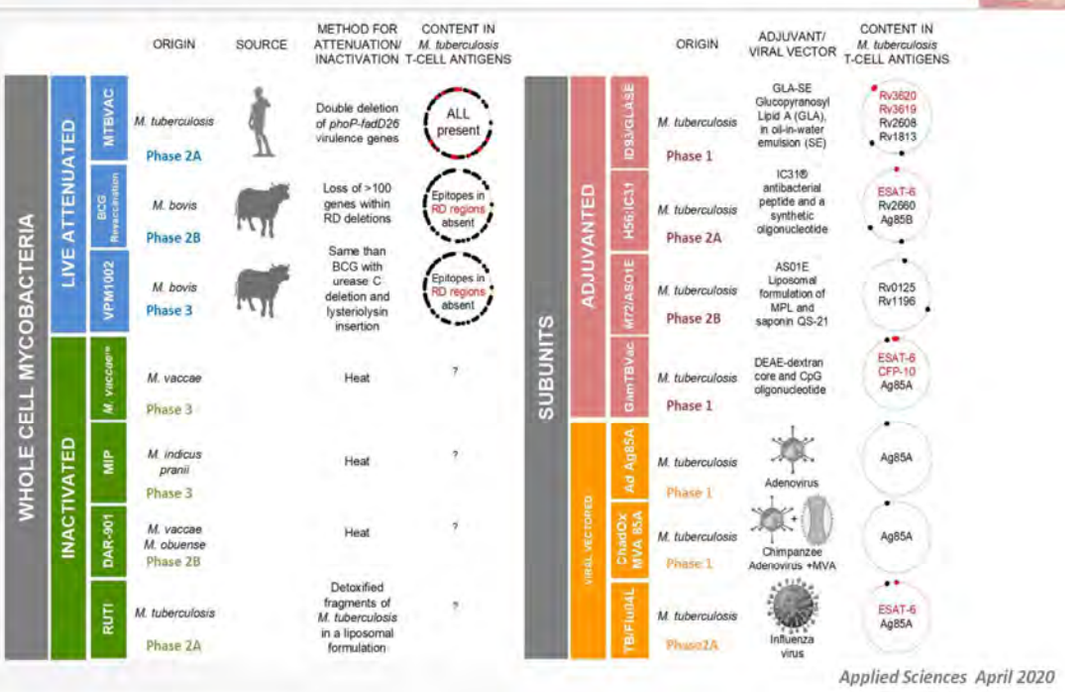
Candidate TB Vaccine Pipeline (WHO Global Report 2021)

: 9 candidates in Phase 2b/3 (POI/POD/POR)

Phase I	Phase IIa	Phase IIb	Phase III
AdHu5Ag85A[b] McMaster, CanSino	ChAdOx185A-MVA85A[b] (ID/IM/Aerosol) University of Oxford	BCG ReVax[c] Gates MRI	GamTBvac[d] Ministry of Health, Russian Federation
AEC/BC02[e] Anhui Zhifei Longcom	ID93 + GLA-SE[d] IDRI, Wellcome Trust, IAVI	DAR-901 booster[e] Dartmouth, GHIT	MIP/Immuvac[e] ICMR, Cadila Pharmaceuticals
	TB/FLU-04L[b] RIBSP	H56: IC31[d] SSI, Valneva, IAVI	MTBVAC[c] Biofabri, TBVI, University of Zaragoza
		M72/AS01E[d] GSK, Gates MRI	VPM1002[c] SIIPL, VPM
		RUTI®[e] Archivel Farma, S.L.	

[a] Information was self-reported by vaccine sponsors to WHO or to the Stop TB Partnership Working Group on New TB Vaccines.

Diversity of the pipeline of TB vaccine candidates in clinical trials



Applied Sciences April 2020

02

Development status of new TB vaccine in Korea

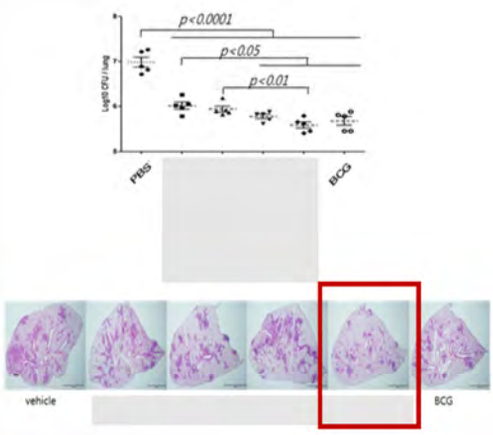
The new TB vaccine pipeline in Korea

Platform	Type of candidate vaccine	Pre-clinical	Phase 1	Phase 2	Phase 3	Developers
Protein subunit	QTP101 (ID93/GLA-SE)					Quratis
Protein subunit	EG-TB(+liposome)			Ongoing Ph2b		EYEGENE Inc.
DNA	GX-170		Ph1 IND			Genexine
mRNA	repRNA+LION					Quratis
Protein subunit	Peptide/mucosal adjuvant					NAVI

GX-170 (DNA vaccine)

◆ **GX-170** : DNA vaccine candidates, including 7 TB antigens, and 3 genetic adjuvants

Prevention of disease vaccine (POD) and Therapeutic vaccine



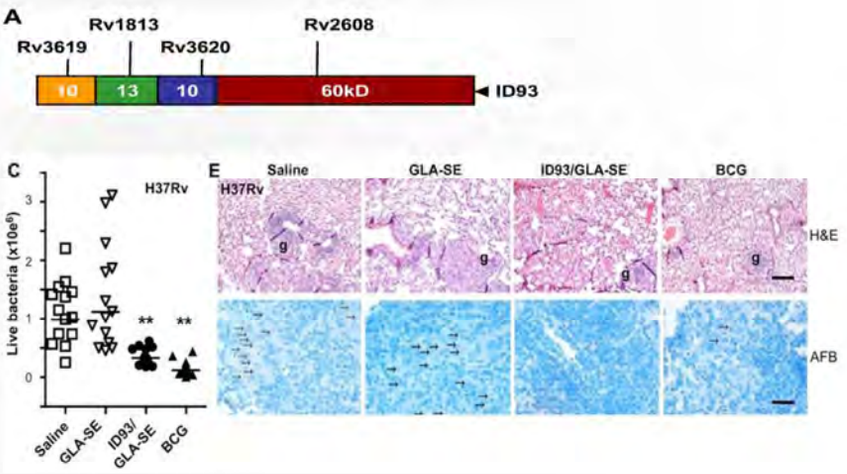
GX-170 Phase 1 trial IND approval

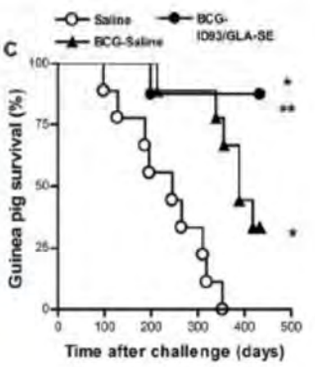
Platform	Type of candidate vaccine	Pre-clinical	Phase 1	Phase 2	Phase 3	Developers
DNA	GX-170		Ph1 IND			Genexine

◆ **Phase 1** : Dose escalation, Evaluate the tolerability, Safety and Immunogenicity of GX-170, a DNA therapeutic vaccine, Administered Intramuscularly by Electroporation (EP), 18-65 yr olds, Patients with Pulmonary tuberculosis who have high risk factor for relapse or Treatment failure

QTP101(ID93/GLA-SE)
- BCG boosting effect

Quratis





Bertholet S et al., Sci Transl Med, 2010

QTP101(ID93/GLA-SE) Phase 2b/3
- BCG boosting effect

Quratis

◆ **Phase 2b/3 : Two-Stage, Randomized, Double-blind, Placebo-Controlled Trial to Evaluate the Efficacy, Immunogenicity and Safety of Quratis` Tuberculosis (TB) Vaccine Candidate QTP101 (ID93 + GLA-SE) against TB in Adolescents and Adult (QFT +/-),** *Not yet recruiting*

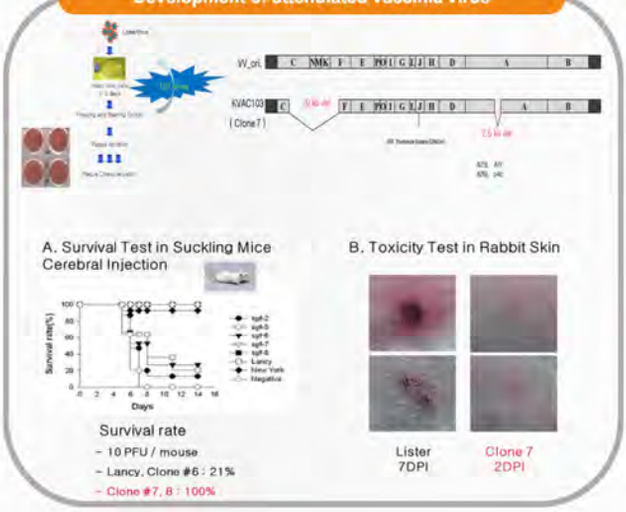
- Stage I : 240 participants in South Korea,

- Stage II : 7,461 participants in Southeast Asia (Indonesia, Philippines, Thailand, etc.) including Korea

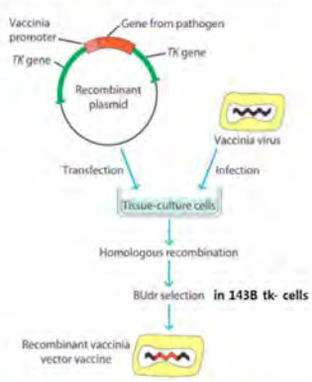
03 The study of viral vector-based TB vaccine candidates

Vaccine candidates by Vaccinia virus vector (KVAC103)

Development of attenulated vaccinia virus



Development of attenulated vaccinia viral vector



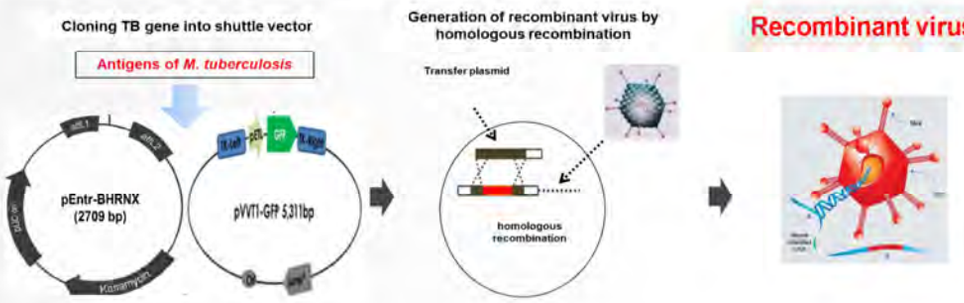
" 0.1% Recombinant Virus "

Construction of recombinant virus expressing TB antigens

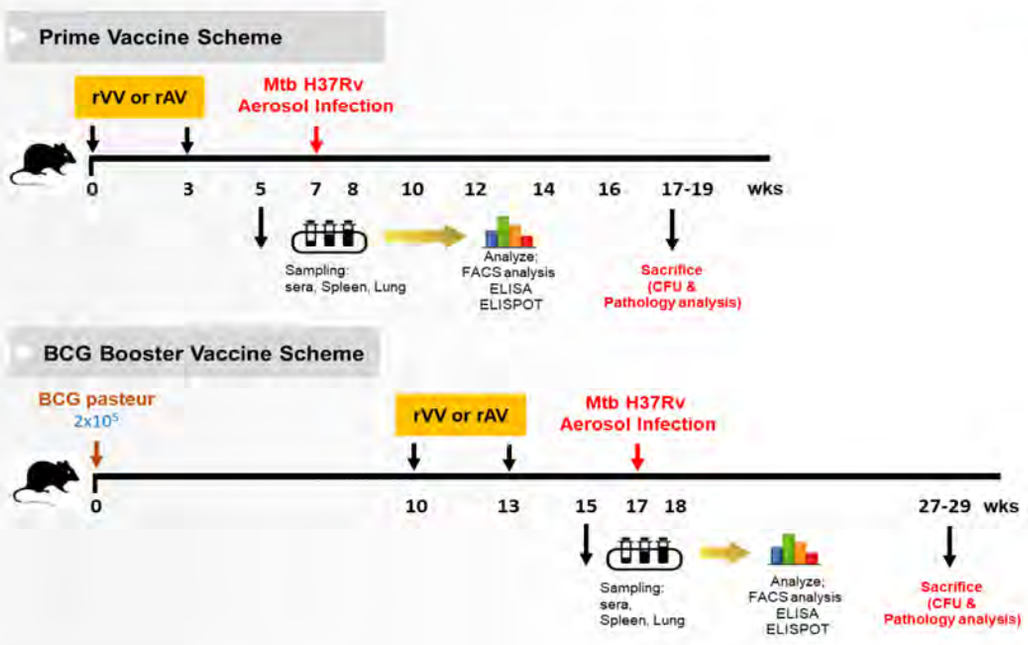
- 7 antigens : active phase 4, latent phase 2, Reactivation phase 1

Antigen Type	Name	Biological function	Antigen Type	Name	Biological function
Active phase	Ag85	Ag85 complex, Required for biosynthesis of the cell wall	Latent phase	HspX	Stationary phase, starvation
	TB10.4	Fuse with Ag85B and represent a more strong protective activity		Rv2660	starvation
	ESAT-6	Early secreted antigenic target-6 Encoded in RD1 region Induced phagocytosis	Resuscitation	RpfE	Promote the resuscitation and growth of dormant
	MPT64	Inhibits apoptosis of infected host macrophage			

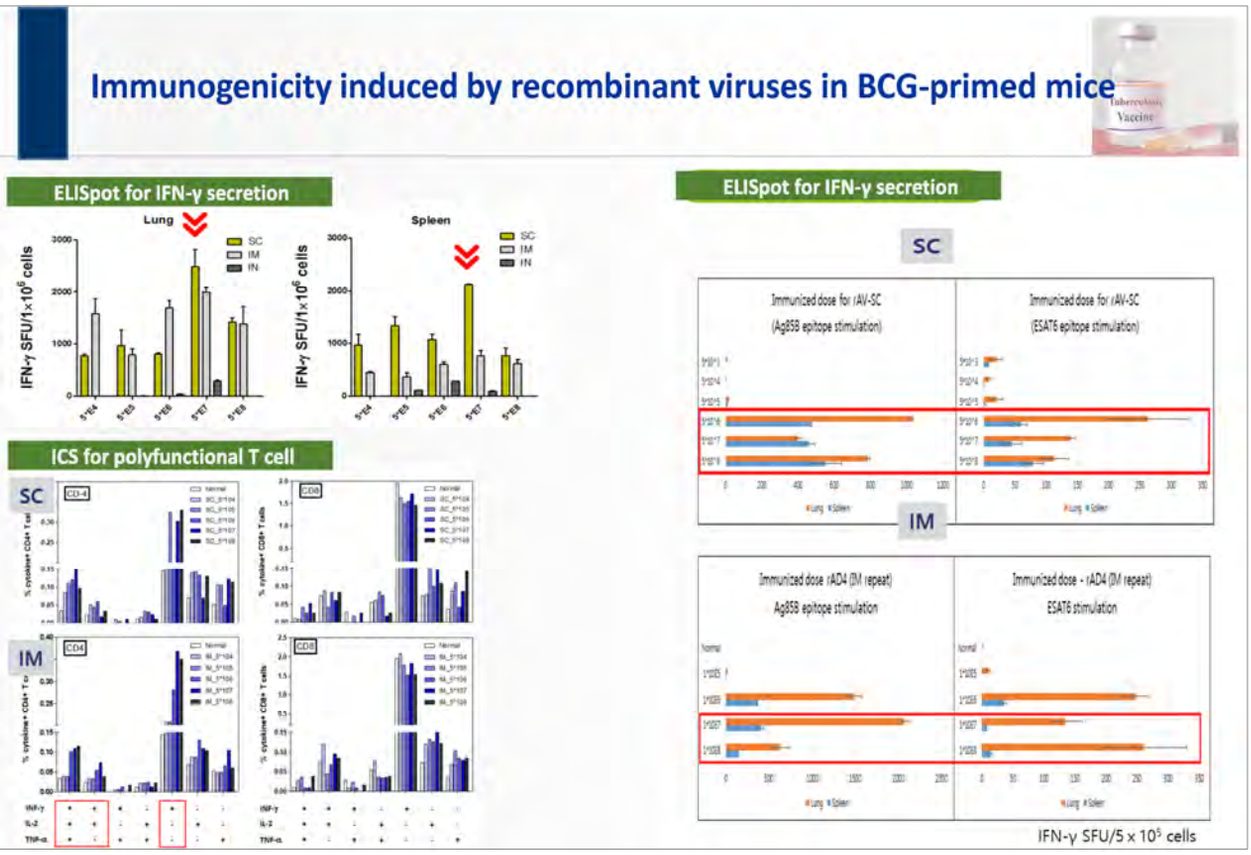
- Multiple antigen fusions : TB10.4-HspX, Ag85B-ESAT6-MPT64-RV2660



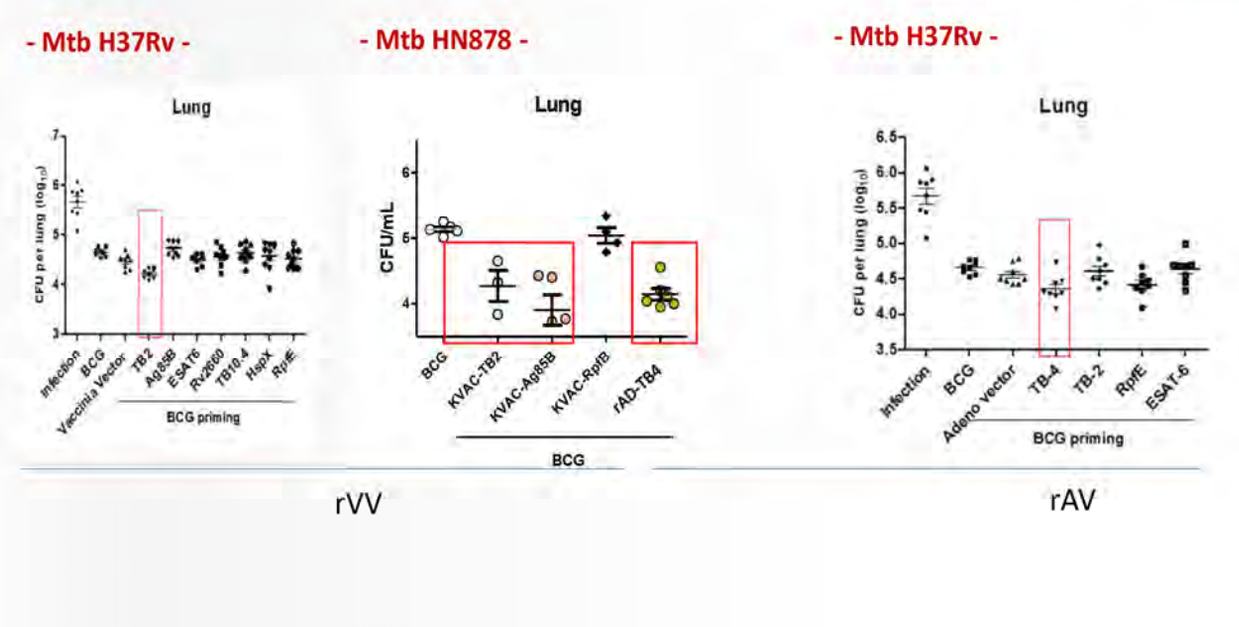
Animal immunization and aerosol infection schedule



Immunogenicity induced by recombinant viruses in BCG-primed mice



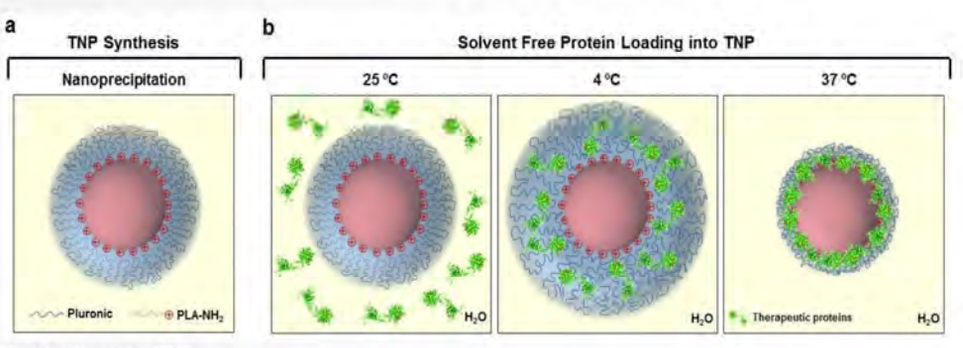
Protective efficacy of recombinant viruses in the M.tb-infected mouse model



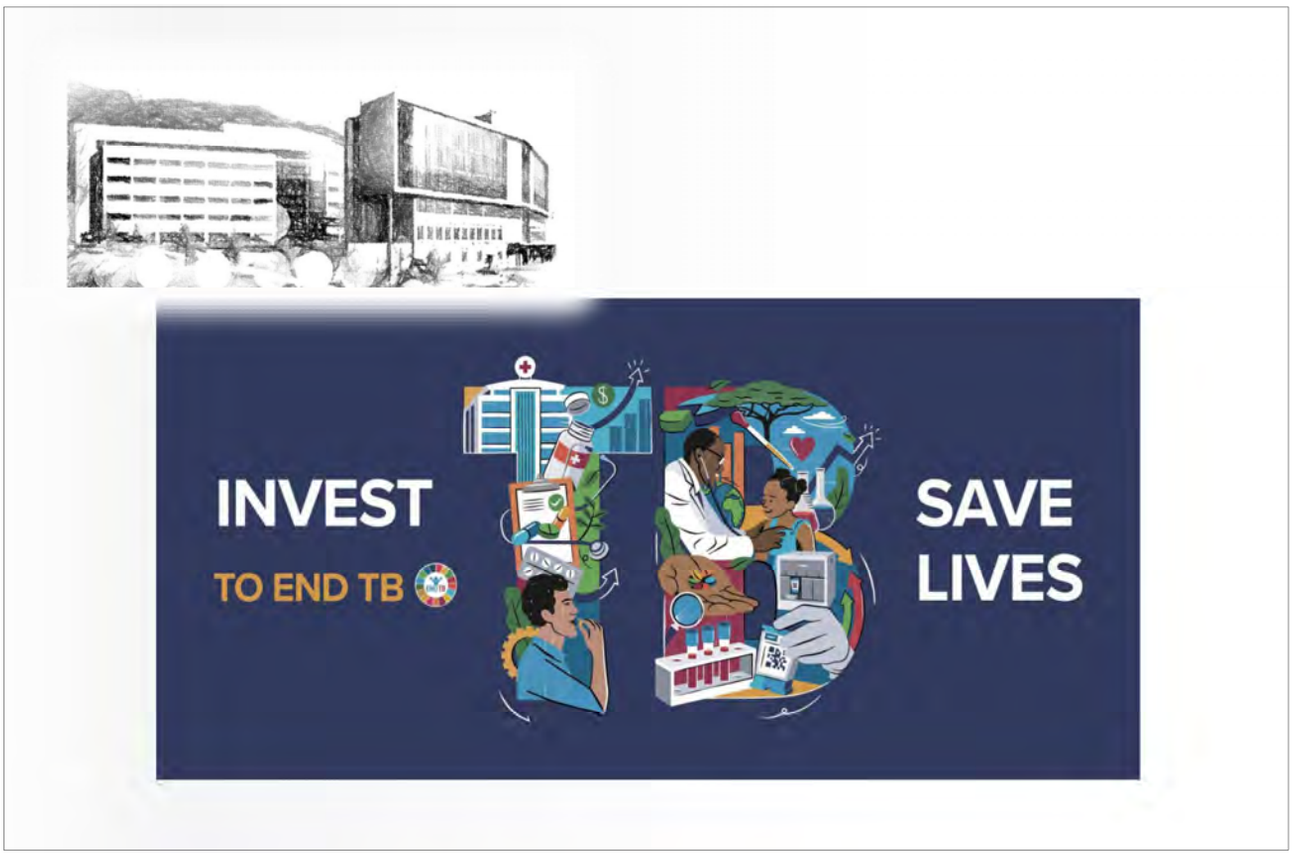
04 Novel platform application

Solvent-free Thermosponge Nanoparticle (TNP) technology

- Nano sponge technology that can efficiently deliver various drugs (hydrophilic/hydrophobic)
  - hydrophilic : protein, peptide, nucleic acid (mRNA, siRNA etc)
  - Hydrophobic : drugs with hydrophobic properties
- Loading drugs without using organic solvents through temperature-sensitive characteristics
- Application range through surface modification (e.g., skin penetration, cancer targeting, etc.)



* Choi et al., Nano Letters (2014)


INVEST
TO END TB
SAVE
LIVES

2. Overview of TB vaccine development

Dr. Rasmus Mortensen (SSI, Denmark)

Rasmus Mortensen

Head of the TB Vaccine Research

Statens Serum Institut, Denmark

- **EDUCATION:**

2015	Ph.D. in Medical Sciences and Immunology, University of Copenhagen Degree date: December 17, 2015
2011	M.Sc. Nanobiotechnology

- **PROFESSIONAL EXPERIENCE:**

2018 ~ current	Head of TB Vaccine Research Statens Serum Institut, Dept. of Infectious Disease Immunology
2015 ~ 2018	Post doc, Host-directed therapy against tuberculosis, Statens Serum Institut, Oslo University Hospital
2012 ~ 2015	Ph.D. University of Copenhagen, Medical Sciences Dept. of International Health, Immunology and Microbiology

- **SUMMARY**

Topic: Overview of TB Vaccine Development

Abstract

Tuberculosis (TB) remains a leading cause of death from infectious diseases and the impact of the COVID-19 pandemic has increased both mortality and the number of cases. Inspired the newest knowledge in TB vaccine development, the Center for Vaccine Research at SSI has developed two subunit vaccines in their TB program, 1) H56:IC31, that is in a Phase IIb trial testing it's efficacy against recurrent TB and 2) H107e/CAF10b, that is a next-generation subunit vaccine designed for synergy with the BCG vaccine. Using new adjuvant technology, this vaccine promotes so-called Th17 cells that are gaining increasing interest in the field for their role in protective immunity. Join this talk by Rasmus Mortensen, Head of TB vaccine Research, and learn more about the two vaccines and SSIs plans for development.

What is tuberculosis?

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- Caused by *Mycobacterium tuberculosis that invades macrophages*
- Evolutionary adapted humans and spreads slowly
- One fourth of the worlds population is infected (or exposed) with TB
  - 5-10% develops active disease
  - 1.6 million annual deaths
- The BCG vaccine protects infants against severe disease, but limited effect against pulmonary TB in adolescents and adults

The TB vaccine H56:IC31 product overview

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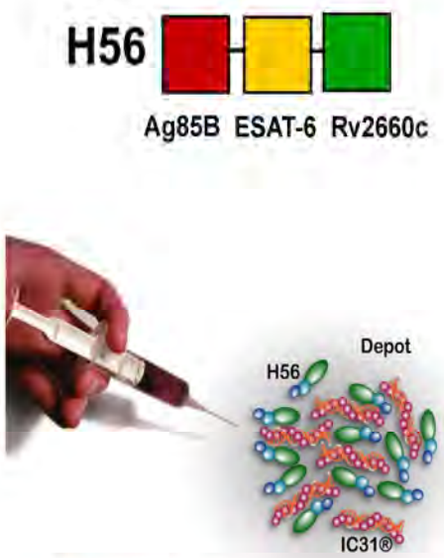
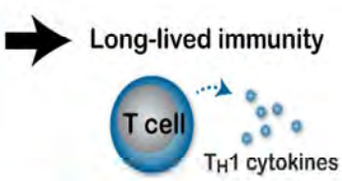


The H56:IC31 multistage vaccine candidate designed to boost BCG and introduce ESAT-6 specific immunity. H56 consists of a fusion protein of three antigens expressed at different stages of Mtb infection and a T helper type 1 cell stimulating adjuvant, IC31® (Valneva).

H56 fusion protein:
Ag85B: An immunodominant antigen secreted in the acute phase of infection
ESAT-6: A premier virulence-associated antigen highly expressed throughout all stages of infection
Rv2660c: A stress-induced antigen, the expression of which is strongly associated with latent TB infection

IC31© adjuvant:
A 2-component adjuvant comprised of an oligodeoxynucleotide ODN1a and a polypeptide KLK, signalling through TLR9



Aagaard Nat Med 2011, Schellack Vaccine 2006, Pattacini PloS One 2012 3

H56:IC31 preclinical support (NHPs)

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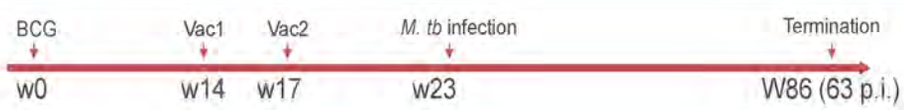
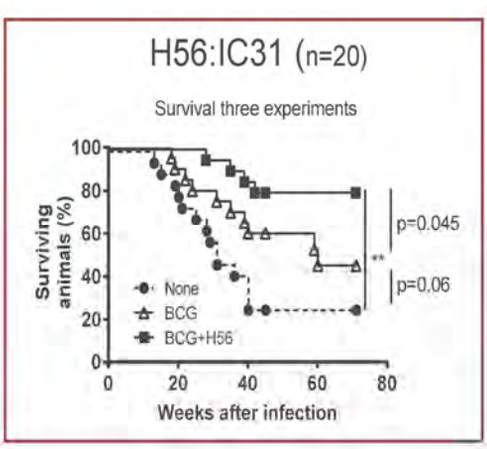


Clinical read-outs
- Clinical disease/weightloss
- X-ray changes
- Temperature
- ESR
- Organ pathology



Phase IIb H56:IC31 POR trial design

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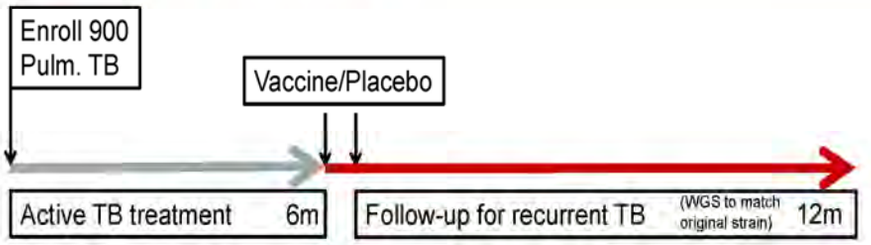

Sites	Mbeya, Tanzania TASK, Aurum, SATVI, UCT Lung, South Africa
Sponsor	AERAS/SSI
Trial duration	6+2+12 months
Vaccine efficacy	60%
Recurrence rate	4% / yr
Loss to follow up	10%
Power	80%
Type I error rate (two-sided)	20%
Sample size/arm	450
Expected prim. endpoints	23
Cost	13.8 million €

Results in fall 2023!

The TB vaccine H56:IC31: clinical development plan

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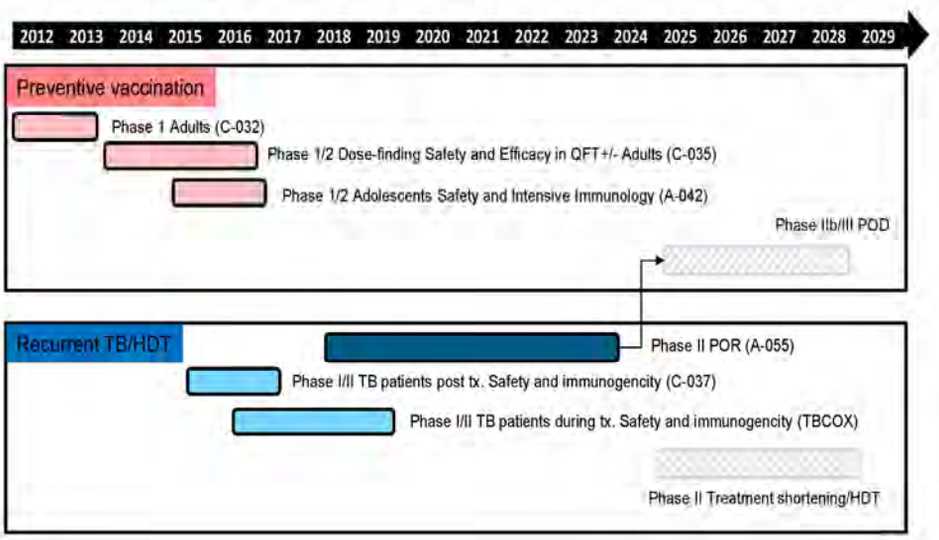

The clinical development strategy is aligned with the Rational Development Strategies for TB vaccines and the Global Portfolio Management Principles for TB vaccine (stage gates) endorsed by major funders and organizations

GOALS FOR FUTURE TB SUBUNIT VACCINES

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1. Improved immunogenicity in humans (e.g. Th1/Th17)
   - Adjuvants
   - Delivery
2. Broader antigen composition
   - Multiple different antigens
   - Highly expressed
   - Recognized in humans

The H107 vaccine - Mtb specific antigens

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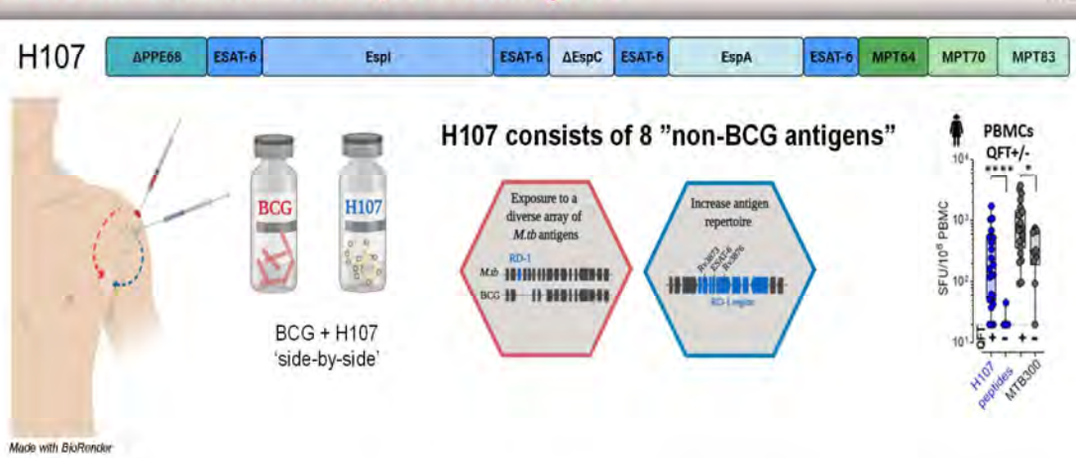

Advantages of BCG co-administration with Mtb-specific subunit:

1. Spare a visit (large practical implications)
2. Adjuvant effect from BCG (potential synergy)
3. Broaden the immune response

The H107 vaccine - Mtb specific antigens

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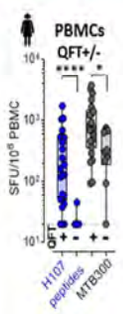
H107 | ΔPPE68 | ESAT-6 | EspI | ESAT-6 | ΔEspC | ESAT-6 | EspA | ESAT-6 | MPT64 | MPT70 | MPT83

BCG + H107
'side-by-side'

H107 consists of 8 "non-BCG antigens"



Advantages of BCG co-administration with Mtb-specific subunit:

1. Spare a visit (large practical implications)
2. Adjuvant effect from BCG (potential synergy)
3. Broaden the immune response (Th17 cells)

Broadening of response phenotype - T cell expansion vs. T cell priming

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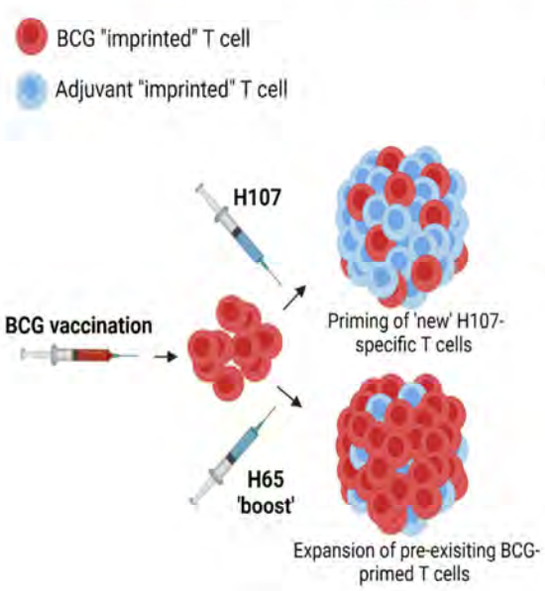
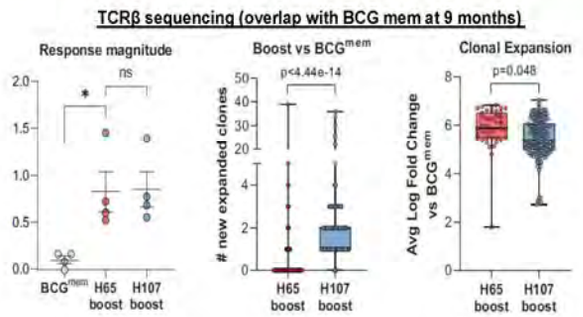
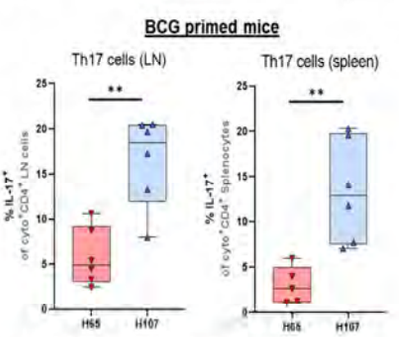
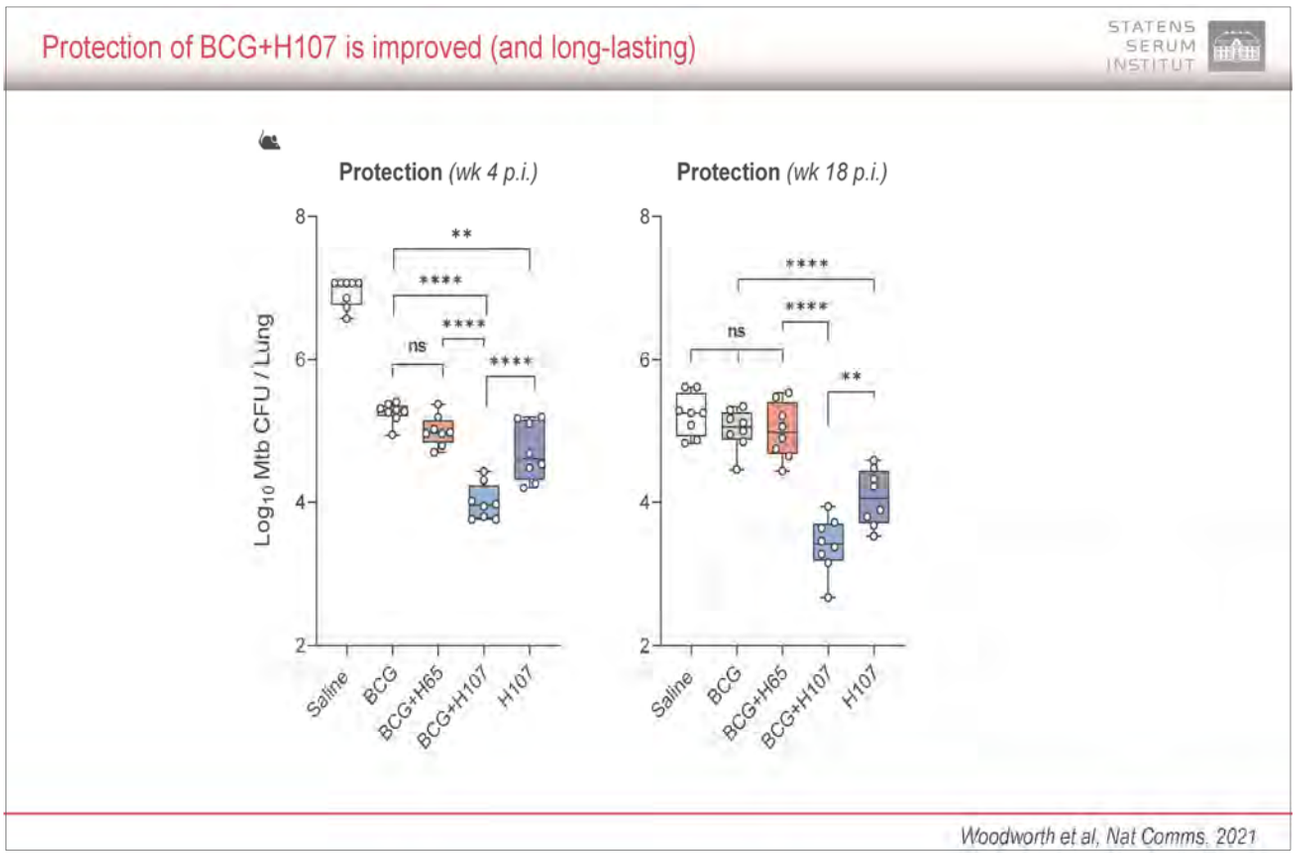






Choice of antigen influences T cell phenotype in a BCG-setting -> H107 favor adjuvant imprinting

Aagaard et al. JI 2020, Woodworth et al, Nat Comms. 2021


Protection of BCG+H107 is improved (and long-lasting)
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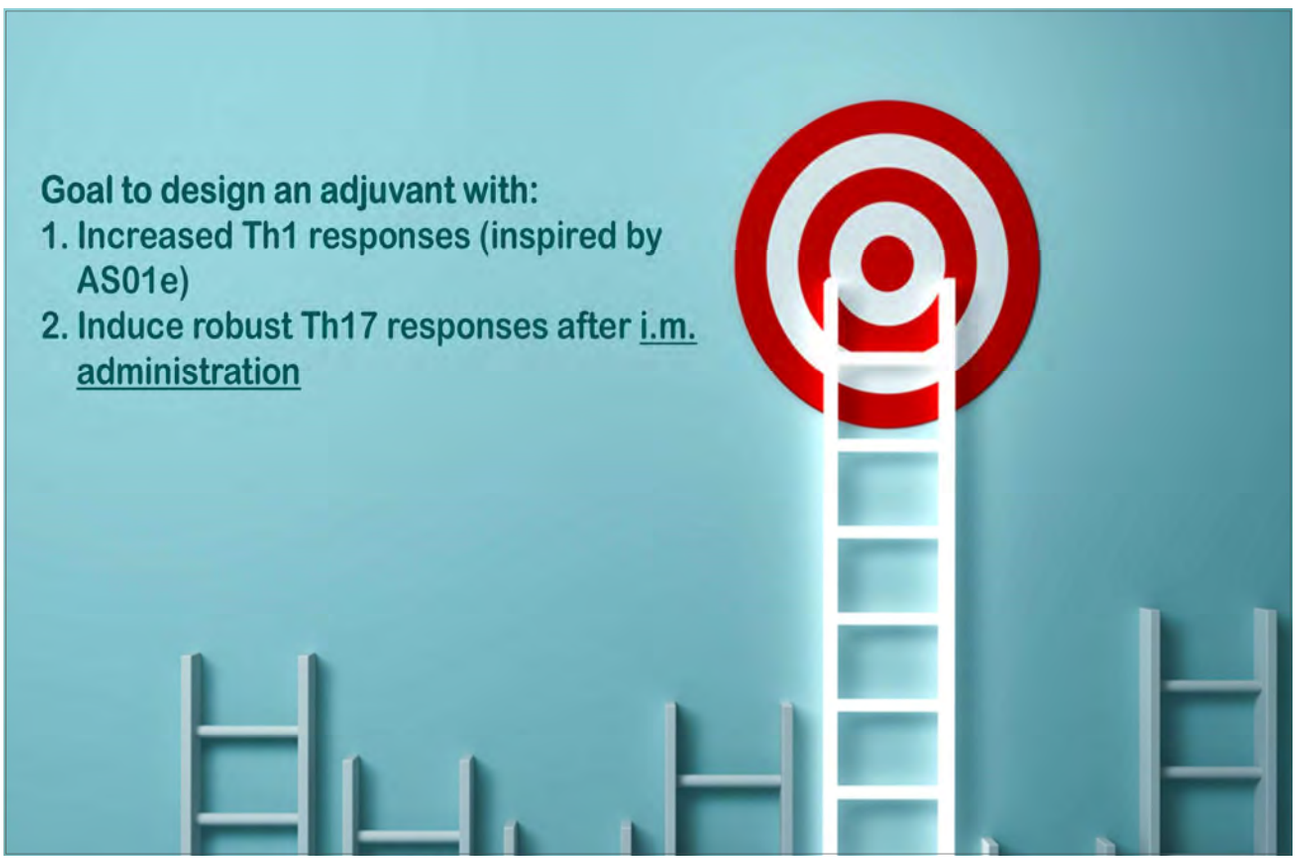
Protection (wk 4 p.i.)
Protection (wk 18 p.i.)
Log10 Mtb CFU / Lung
Saline
BCG
BCG+H65
BCG+H107
H107
ns
**
****
Woodworth et al, Nat Comms, 2021


Goal to design an adjuvant with:
1. Increased Th1 responses (inspired by AS01e)
2. Induce robust Th17 responses after i.m. administration

Head-to-Head comparison of CAF® adjuvants

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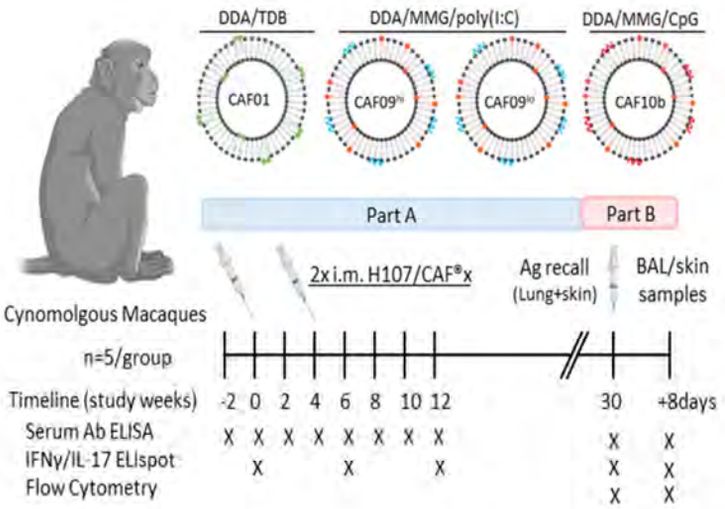

Roger LeGrand, CEA, Paris

Unpublished, manuscript in prep w. LeGrand group

CAF®10b confer increased Th1/Th17 memory in NHPs (but not mice)

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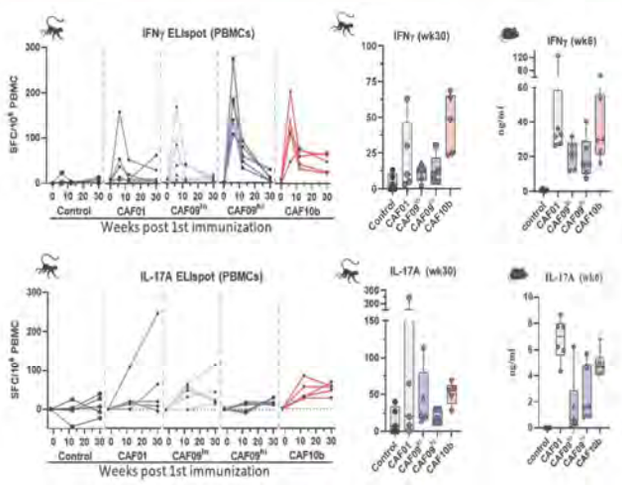

- Peak response does not necessarily reflect the memory response (CAF®09hi vs. CAF®10b)
- CAF®10b gives a robust Th17 response (CAF®09hi does not)
- Immunogenicity in mice and NHPs is different -> adjuvants can be species specific!

Unpublished, manuscript in prep w. LeGrand group

H107/CAF®10b display robust recall responses in the lung

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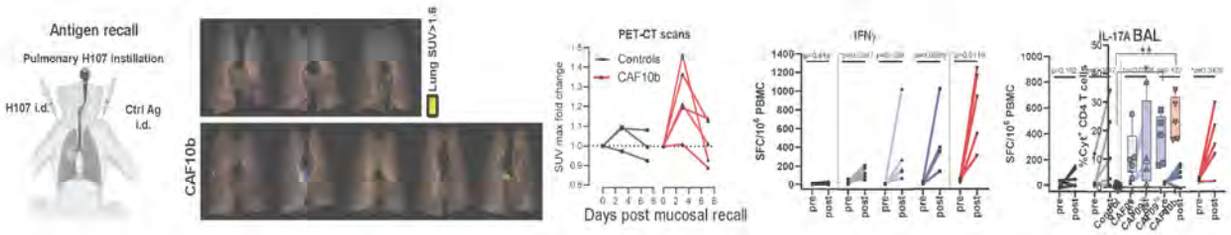

- Local recall inflammation is short-lived (potential for *in vivo* antigen recall in humans)
- Vaccine-induced Th1 and Th17 cells expand significantly in response to antigen recall (CAF®10b responses 5-10 fold higher than CAF®01)
- Mucosal recall responses were highest for CAF®10b (~20% H107-specific T cells in BAL)
- -> GMP manufacturing and clinical testing in 2023

Unpublished, manuscript in prep w. LeGrand group

Phase Ia – Safety of H107/CAF10b + intranasal Ag recall in IGRA- participants

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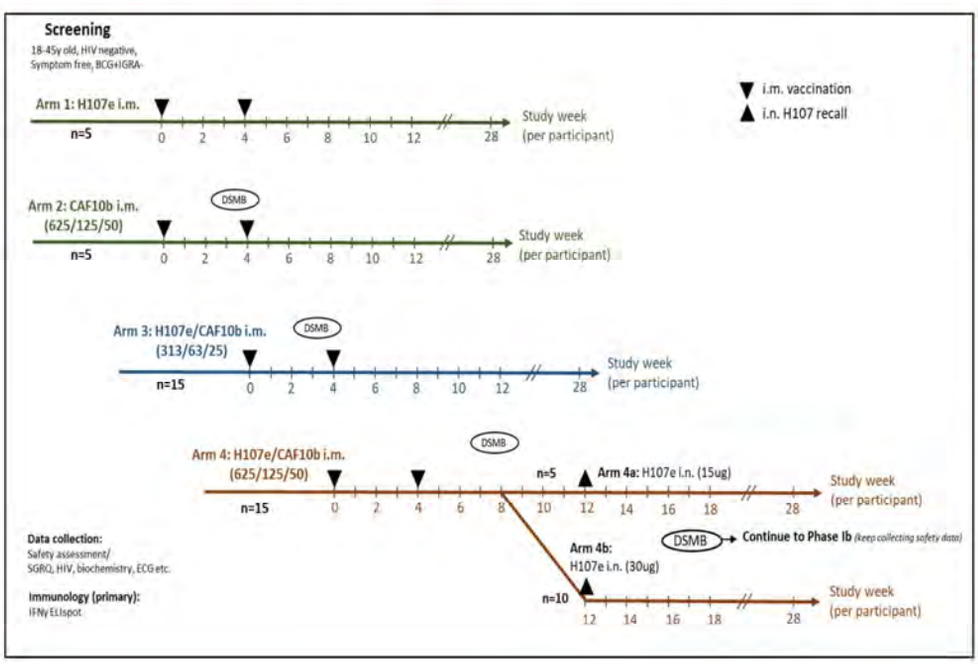

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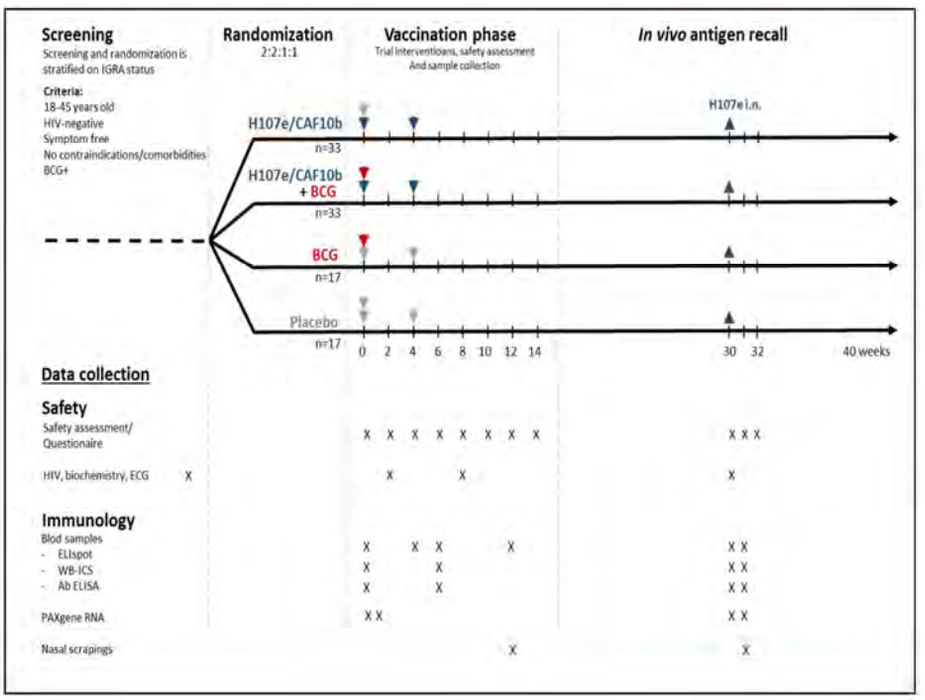
Phase Ib – Safety and immunogenicity of H107/CAF10b +/- BCG co-administration



Acknowledgements

TB Vaccine Research

Rasmus Mortensen
Joshua Woodworth
Thomas Lindenstrøm
Ming Liu Olsen
Camilla Myhre Maymann
Nafsika Panagiotopoulou
Bezawit Alemayehu
Karin Dijkman

Adjuvant Research

Dennis Christensen
Gabriel K. Petersen

Human Immunology

Alvaro Borges
Per Skallerup

TB Vaccine Development

Charlotte Jensen
Grith Krøyer Wood

Collaborators/partners

Churchyard, Beattie; Aurum Inst.
Scriba/Nemes and colleagues; SATVI/UCT
Joosten/Ottenhof/Visser, LUMC
Urdahl; Seattle Children's Research Inst.
Le Grand; CEA,
Lindestam Arlehamn, LaJolla inst. Imm.
Frank Verreck, BPRC
Dyrhol-Riise; Oslo University Hospital
Simon Clark, Public Health England
Behr; McGill Univeristy
C. King, Univ. Basal
O. Neyrolles, IPBS

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