제24회 한·미·일 환태평양 국제컨퍼런스EID
24th International Conference on Emerging Infectious Diseases in the Pacific Rim

Pandemic preparedness and the rapid emergence of pathogens caused by global environmental change

2024 International Symposium for Infectious Diseases Research Institutes Cooperation

감염병연구기관 국제심포지엄

2024. 3. 8(금) 08:30~16:00 그랜드하얏트 인천

온-오프라인 동시 진행

질병관리청
국립보건연구원 국립감염병연구소

2024
감염병연구기관 국제심포지엄
International Symposium for Infectious Diseases Research Institutes Cooperation

Time(KST)	Program	
08:30~09:00	**Registration**	
09:00-09:15	Welcoming Remarks(KDCA)	**Jee, Young-mee** (Commissioner, Korea Disease Control and Prevetion Agency)
	Opening Remarks(KNIH)	**Park, Hyun-Young** (Director, Korea National Institute of Health)
	Congratulatory Remarks(KNID)	**Jang, Hee-Chang** (Director, Korea National Institute of Infectious Diseases)
09:15-09:25	[Keynote speech 1] Development Strategies and Plans for the Therapeutics within 100/200 Days in Preparation for the Novel Infectious Disease Pandemic	**Kim, Kyung-Chang** (Director, KNIID Emerging Virus Research Center)
09:25-09:35	[Keynote speech 2] Development Strategies and Plans for the Vaccines within 100/200 Days in Preparation for the Novel Infectious Disease Pandemic	**Lee, Yoo-Kyung** (Director, KNIID Vaccine Research Center)
Session 1. Characteristics of Emerging Infectious Diseases and clinical studies **Chair: Park, Man-Seong(Professor, Korea University)**		
09:35-09:50	Age-depedent differential pathogenesis of SFTSV infections	**Choi, Young-Ki** (Director, Korea Virus Research Institute)
09:50-10:05	Deglycosylation of human influenza A virus (H3N2) hemagglutinine increases virulence in mice.	**Choi, Jang-Hoon** (Research officer, KNIID)
10:05-10:20	Clinical presentation and viral shedding in patients with Mpox in South Korea	**Kim, Min-kyung** (Professor, National Medical Center)
10:20-10:35	Long COVID Research Project in South Korea : What we've learned about long COVID	**Lee, Ja-Cob** (Professor, Hallym University)
10:35-10:45	Q&A	
10:45-11:00	Break	
Session 2. Current status and strategies for the development of therapeutics for Emerging Infectious Diseases **Chair: Kim, Ki-Soon(Professor, Korea University)**		
11:00-11:15	Platforms & Tools to Enable Rapid Pandemic Response	**Dimitri Lavillette** (Chief Scientific Officer, Institut Pasteur Korea)
11:15-11:30	Development of SARS-CoV-2 S2 Targeted Vaccines and Therapeutic Antibodies	**Cho, Eun-Wie** (Director, Korea Research Institute of Bioscience and Biotechnology)
11:30-11:45	Lessons from COVID-19 for the development of antiviral drugs	**Han, Soo-Bong** (Director, Korea Institute of Chemical Technology)
11:45-12:00	Acceleration of drug discovery with AI	**Kim, Woo-Youn** (Professor, Korea Advanced Institute of Science and Technology)
12:00-12:10	Q&A	
12:10-13:00	Lunch	

Time(KST)	Program	
Session 3. Outstanding Achievements in the Development of Vaccines for Emerging Infectious Diseases **Chair: Seong, Baik-Rin(Professor, Yonsei University)**		
13:00-13:15	Rapid screening of target antigenic sites for SARS-CoV-2 vaccine development using Fv-antibody library	**Pyun, Jae-Chul** (Professor, Yonsei University)
13:15-13:30	HAs-NAu strategy for the development of better influenza vaccines	**Kim, Jin-Il** (Professor, Korea University)
13:30-13:45	SFTS mRNA Vaccine Research and Development	**Kim, Hyeon Guk** (Research officer, KNIID)
13:45-14:00	Broad Spectrum Vaccine and mAbs for Sarbecoviruses	**Wang Linfa** (Professor, DUKE-NUS, Singapore Executive Director for the Programme for Research in Epidemic Preparedness and Response (PREPARE), Singapore)
14:00-14:10	Q&A	
14:10-14:25	Break	
Session 4. Current Status and Strategies in the Development of Vaccines for Emerging Infectious Diseases **Chair: Hong, Kee-Jong(Professor, Gachon University)**		
14:25-14:40	Vaccine adjuvant platform	**Yeom, Jeong-Seon** (CEO, CHA Vaccine Institute)
14:40-14:55	SKY mRNA Platform for Prophylactic Vaccine Development	**Jinan Shin** (Vice President, SK bioscience)
14:55-15:05	Research and Development Strategy for RSV Vaccine	**Kim Seok-Kyu** (Director, U Biologics)
15:05-15:15	Strategy to develop effective multivalent COVID-19 vaccines against emerging variants based on adenovirus vector platform	**Kang, Chang-Yul** (CEO, CELLID)
Panel Discussion **Chair: Seong, Baik-Rin(Professor, Yonsei University)**		
15:15-15:55	Q&A and Future Collaboration Prospects 〈Therapeutics〉 - Kim, Kyung-Chang, Dimitri Lavillette, Han, Soo-Bong, Kim, Woo-Yeon 〈Vaccines〉 - Lee, Yoo-Kyoung, Yeom, Jeong-Seon, Kim Seok-Kyu, Kang, Chang-Yul	
15:55-16:00	Closing Remarks(KNIID)	**Jang, Hee-Chang** (Director, Korea National Institute of Infectious Diseases)

Welcoming Remarks(KDCA)

Youngmee Jee

Commissioner

Korea Disease Control and Prevention Agency

EDUCATION:

Ph.D, Virology, University of London, United Kingdom, 1997

Diploma, Medical Microbiology, University of London, United Kingdom, 1988

MD, Seoul National University Medical School, Republic of Korea, 1986

WORK HISTORY:

Public Sector

Commissioner

Korea Disease Control and Prevention Agency

December 2022-Present

Director-General

Center for Infectious Disease Research, Korea Centers for Disease Control and Prevention, Ministry of Health and Welfare

May 2017-October 2019

Director-General

Center for Immunology and Pathology, Korea Centers for Disease Control and Prevention, Ministry of Health and Welfare

October 2014-May 2017

Regional Coordinator

Expanded Programme on Immunization, Western Pacific Regional Office,

World Health Organization (WHO)

August 2007-October 2014

Director

Hepatitis and Polio Viruses Team, National Institute of Health,

Ministry of Health and Welfare

October 2005–August 2007

Director

Division of Enteroviruses, Department of Virology, National Institute of Health,

Ministry of Health and Welfare

December 2003–October 2005

Deputy Scientific Director

Division of Enteroviruses, Department of Virology, National Institute of Health,

Ministry of Health and Welfare

July 1997–December 2003

○ Private Sector

Chief Executive Officer

Institute Pasteur Korea

January 2021–December 2022

President

Korean Society for Microbiology

January 2021– December 2021

Special Advisor to the Prime Minister

Health Affairs

November 2020–April 2021

Visiting Professor

Graduate School of Public Administration, Seoul National University

June 2020–May 2021

Special Representative for Health Diplomacy

Korea Foundation

April 2020–Present

Member

WHO International Health Regulation Emergency Committee on COVID-19

January 2020–Present

President

Korean Society of Infectious Diseases

December 2017–November 2019

Member

WHO Strategic Advisory Group of Experts for Immunization (SAGE)

April 2017–April 2020

Member

Board of Trustees of the International Vaccine Institute (IVI)

January 2016–December 2019

AWARDS:

President's Service Merit Medal

2017

Prime Minister's Commendation

in recognition of the contribution to infectious disease management projects

2005

Opening Remarks(KNIH)

Hyun-Young Park

- Director (Deputy Minister)
- Korea National Institute of Health

EDUCATION:

- 2000 Yonsei University College of Medicine (Ph.D.)
- 1995 Yonsei University College of Medicine (M.S.)
- 1990 Yonsei University College of Medicine (M.D.)

PROFESSIONAL EXPERIENCE:

- 2023 ~ Present Director, Korea National Institute of Health
- 2020 ~ 2023 Director, Department of Precision Medicine, KNIH
- 2018 ~ 2020 Director, Center for Genome Science, KNIH
- 2017 ~ 2018 Director, Division of Cardiovascular Diseases, KNIH, KCDC
- 2012 ~ 2023 PI, National Research Program for Women's Health
- 2011 ~ 2014 Team leader, National Center for Medical Information and Knowledge TF
- 2008 ~ 2014 Team leader, Clinical Research Coordination TF
- 2005 ~ 2017 Director, Division of Cardiovascular & Rare Diseases, KNIH, KCDC
- 2002 ~ 2003 Research Associate, Duke University Medical Center, USA
- 2004 ~ 2005 Assistant professor of Cardiology (Dept. of internal medicine)
- 2000 ~ 2002 Assistant professor of Cardiology (Dept. of internal medicine)
- 2000 ~ 2005 Assistant professor, Yonsei Cardiovascular Research Institute
- 1998 ~ 2000 Instructor, Yonsei Cardiovascular Research Institute, Yonsei University College of Medicine
- 1996 ~ 1998 Research Student, Department of Clinical Pathology, Shimane Medical University, Japan
- 1995 ~ 1996 Research fellow, Cardiology division, Yonsei Cardiovascular Center, Yonsei University College of Medicine
- 1990 ~ 1995 Resident, Department of Internal Medicine, Yongdong Severance Hospital

Congratulatory Remarks(KNID)

Hee-Chang Jang

- National Institute of Infectious Diseases (NIID), Korea National Institute of Health (KNIH), Korea Disease Control and Prevention Agency (KDCA)
- Director, National Institute of Infectious Diseases (NIID)

EDUCATION:

- 2017 Chonnam National University, Ph.D
- 2005 Seoul National University College of Medicine, M.M.Sc
- 2000 Seoul National University College of Medicine, M.D.

PROFESSIONAL EXPERIENCE:

- 2020 ~ Present Director, National Institute of Infectious Disease
- 2017 ~ 2019 Post-Doc/Research Fellow, Harvard Medical School / Massachusetts General Hospital
- 2009 ~ Present Professor (tenured), Infectious Disease, Chonnam National University & Chonnam National University Hospital
- 2008 ~ 2009 Fellow, Infectious Disease, Seoul National University Hospital
- 2000 ~ 2008 Volunteer Doctor, Korea International Cooperation Agency (KOICA)
- 2000 ~ 2015 Intern & Resident, Internal Medicine, Seoul National University Hospital

목 차

목 차

세션 3. 신종감염병 백신개발 우수성과

세션 4. 신종감염병 백신개발 현황 및 전략

기조강연 1.

신종감염병 대유행 대비 100/200일 치료제 개발전략 및 계획

2024
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Keynote speech 1

Kyung-Chang Kim

- Division of Emerging Virus & Vector Research
  Center for Emerging Virus Research
  Korea National Institutes of Infectious Diseases
- Director of Division

EDUCATION:

- 2000 B.Sc. (Molecular Biology), Pusan National University
- 2002 M.Sc. (Molecular Biology), Pusan National University
- 2011 Ph.D. (Molecular Biology), Korea University

PROFESSIONAL EXPERIENCE:

- 2020 ~ Present Division Director,
  Division of Emerging Virus & Vector Research
  National Institutes of Health, Korea DCA
- 2021 ~ Present Director of Therapeutics Research and Development Team,
  Central Disease Control Headquarters Treatment and Vaccine Development Task Force
- 2018 ~ Present Board Member, Korean Society for AIDS (2018~)
  Board Member, Korean Society for Virology (2022~)
- 2012 ~ 2015 Post.doc follow, University of Northwestern, U.S
- 2004 ~ 2020 Senior Staff Scientist & Staff Scientist
  Korea National Insitutes of Health (KNIH)

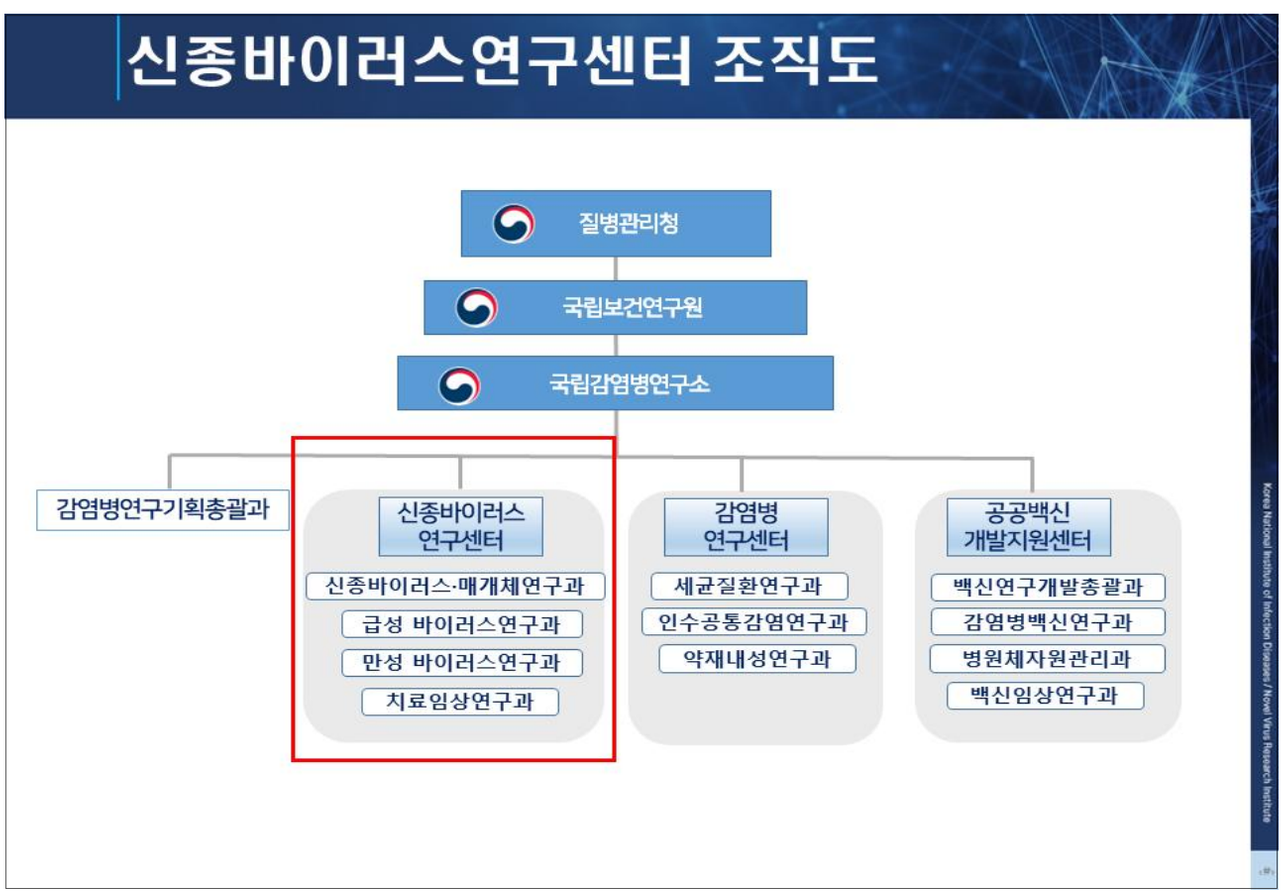
Topic

R&D Strategies and Plan for 100/200 Days Therapeutics Development in Preparation and Response to Emerging Infectious Disease

Abstract

After entering the 21st century, various infectious diseases have been occurring almost every 1-2 years. With the advancement of transportation and the increase of international travelers, the inflow possibility of emerging infectious diseases is gradually increaed. The COVID-19 pandemic has led to large-scale casualties, emphasizing the government's role in the development of treatments and vaccines around the globe. During a pandemic outbreak, treatment serves as the best means of protecting the population until vaccines are secured. To effectively responding future infectious disease outbreaks, proactive preparation and development strategies for therapeutics are urgently needed. Therefore, the KDCA has collaborated across ministries to plan a “Mid- to Long-Term Preparedness and Response Plan for Emerging Infectious Disease” and has devised concrete implementation measures. Through this plan for emerging infection, we introduce present development strategies for priority pathogens for next pandemic.


신종감염병 대유행 대비
100/200일 치료제 개발
전략 및 계획
신종바이러스연구센터
신종바이러스매개체연구과
김경창
질병관리청
국립보건연구원 국립감염병연구소


신종바이러스연구센터 조직도
질병관리청
국립보건연구원
국립감염병연구소
감염병연구기획총괄과
신종바이러스 연구센터
신종바이러스·매개체연구과
급성 바이러스연구과
만성 바이러스연구과
치료임상연구과
감염병 연구센터
세균질환연구과
인수공통감염연구과
약재내성연구과
공공백신 개발지원센터
백신연구개발총괄과
감염병백신연구과
병원체자원관리과
백신임상연구과
Korea National Institute of Infection Diseases / Novel Virus Research Institute

신종바이러스연구센터 추진방향

비전 국가 바이러스 감염병 대응 연구 선도 및 전주기 지원

목표 바이러스 감염병 제어를 위한 핵심기술 및 연구역량 고도화

추진 전략

1] 바이러스 감염병 대응 핵심기술 고도화

2] 치료제 비임상 파이프라인 강화

3] 감염병 임상연구체계 강화

4] 국내·외 협력 및 인프라 강화

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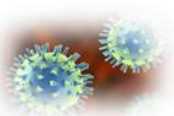
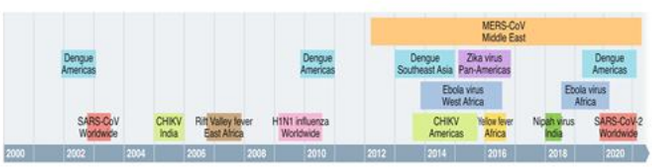
글로벌 감염병 위기 지속

√ 21세기 바이러스성 감염병 이슈





√ 미해결, 신변종바이러스 위협 상존

글로벌 시대, 감염병 안전지대는 없다.

코로나19로 인한 전세계 경제손실 → 13.8조 달러 (IMF, 2022년)

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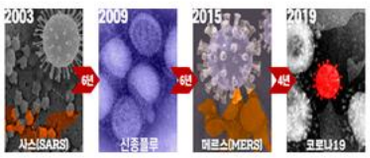
신종감염병 대유행 대비 중장기 계획 발표(23.5)

발생 주기는 짧아지고,
피해는 커지는 팬데믹 위험 상존



- 코로나19 다음 대유행 감염병 후보는 조류인플루엔자(AI) 인체감염증
  전 US CDC director, 글로벌 바이오포럼 2021, '21.11
- Disease X로 인한 재난적 감염병 유행은 고 병독성 RNA 바이러스의 인수공통 전파로 인해 발생할 것
  라셋, '20.5월
- 앞으로 20년 이내 또 다른 팬데믹 발생 가능
  빌 게이츠

[신종감염병 대유행 대비 중장기계획 10대 핵심과제]

감시·예방	① 감염병 조기경보를 위한 통합 감시체계 구축
	② 글로벌 보건안보 선도 및 국제협력체계 강화
대비·대응	③ 세계에서 인정받은 조기 대응역량 지속 발전
	④ 日 확진자 100만명 대응가능한 의료체계 구축
	⑤ 대규모&장기 유행에 흔들리지 않는 필수인력 확보
	⑥ 감염에 취약한 시설·집단을 안전하게 보호
기반	⑦ 협력적·효율적 위기대응 위한 튼튼한 기반 조성
	⑧ 고도화된 정보시스템 및 빅데이터 플랫폼 구축
회복	⑨ 피해완화와 조기 회복을 위한 두터운 지원체계
연구개발	⑩ 백신·치료제 개발 가속화를 위한 R&D 지원체계를 혁신

(필요성) 빠른 치료제 개발 및 공급으로 감염병 위험과 사회·경제적 충격 최소화

(목 표) 신종감염병 발생 100/200일 이내 치료제 개발 및 공급 가능한 대비, 대응, 평가 체계 구축

대비단계
- 우선순위선정
- 라이브러리
- 플랫폼 구축

대응단계
100/200일 내 반응
- 신속개발
- 생산 및 다기관 협력
- 임상 및 비임상 지원

평가· 보완 단계
- 치료제 적용 효능평가
- 변이 대응 유효성 분석
- 거점 실험실 확충

Korea National Institute of Infection Diseases / Novel Virus Research Institute

글로벌 팬데믹 대비 감염병 치료제 확보 프로젝트

KNIID (국립감염병연구소) | CEPI CEPI (감염병혁신연합) | NIH NIAID (미국 국립알레르기전염병연구소)

프로젝트	신종감염병 대유행 대비 중장기계획(23.5)	100 day mission (21.11)	프로젝트 NextGen (23.8)	팬데믹 대비 계획 PPP(21.12) *PANDEMIC PREPAREDNESS PLAN
목표	팬데믹 위기 시 100/200일 초고속 치료제 개발	WHO 비상사태(PHEIC) 선언 후 100일 이내 치료제 확보	미래 팬데믹 발생 대비 미국 정부의 백신 및 치료제 개발	팬데믹 우려 RNA 바이러스과 항바이러스제 표적약물 발굴 플랫폼
우선순위 병원체	6개 바이러스 과 (8종 바이러스) 라싸, SFTS, 코로나19, MERS, 뎅기, 니파, 조류인플루, RSV	25개 바이러스 과 호흡기바이러스과 대상 저분자항바이러스제 25개 후보 확보 (임상 1상 완료)	코로나19 변이주 또는 미래 팬데믹 감염병 흡입형(점막형), long-lasting 백신 또는 항체치료제	7개 바이러스 과 Bunyaviridae, Coronaviridae Filoviridae, Flaviviridae, Paramyxoviridae, Picornaviridae, Togaviridae

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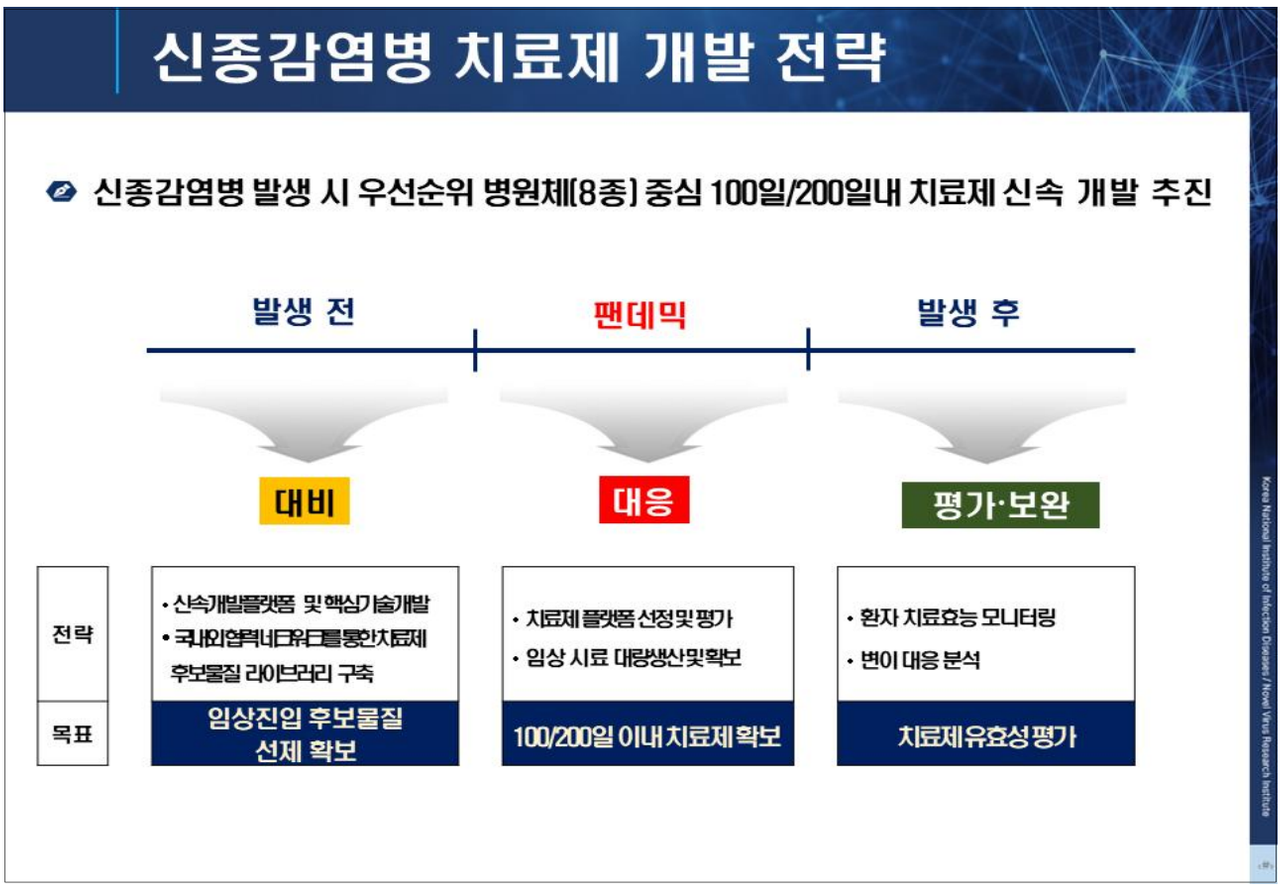
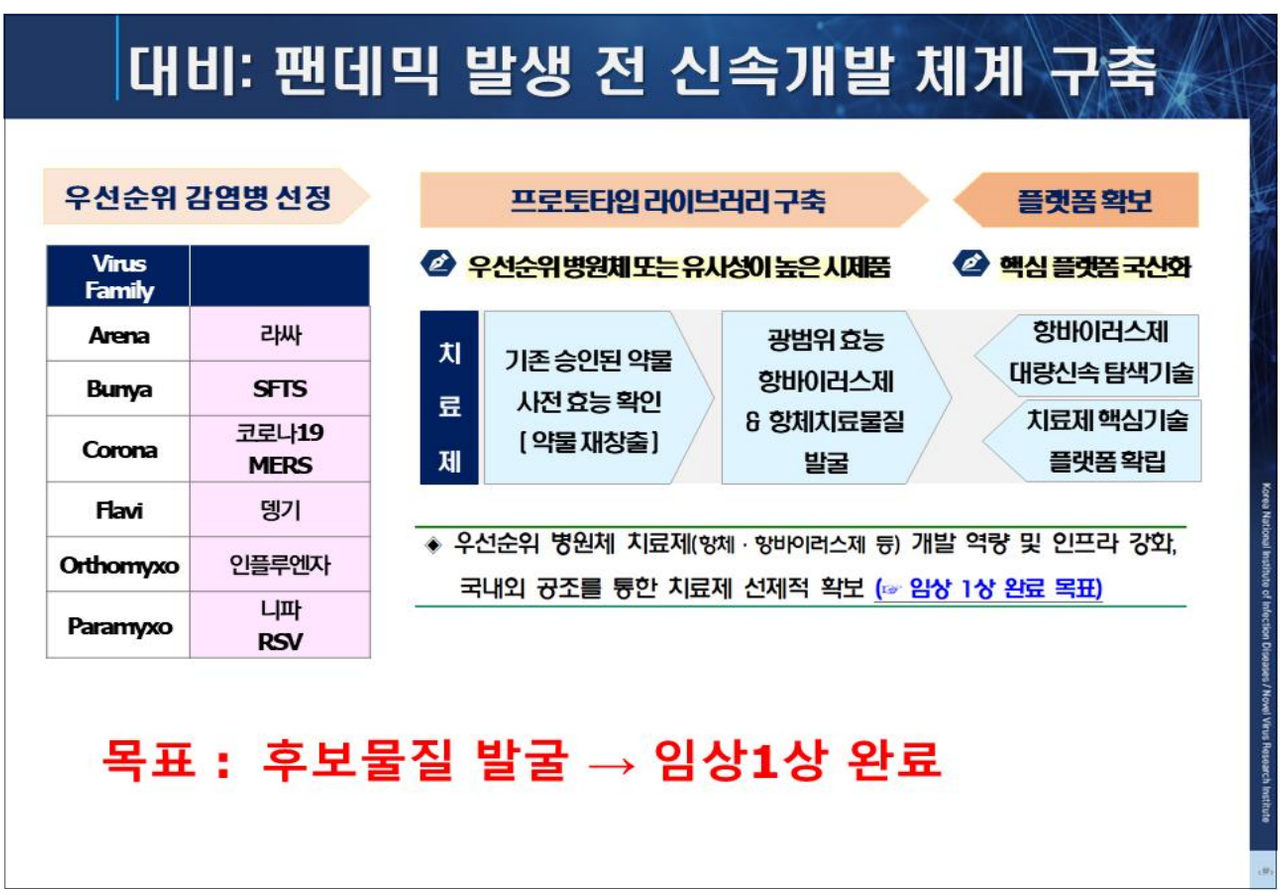

신종감염병 치료제 개발 전략
신종감염병 발생 시 우선순위 병원체(8종) 중심 100일/200일내 치료제 신속 개발 추진
발생 전
팬데믹
발생 후
대비
대응
평가·보완
전략
• 신속개발플랫폼 및 핵심기술개발
• 국내외협력네트워크를통한치료제 후보물질 라이브러리 구축
• 치료제 플랫폼 선정 및 평가
• 임상 시료 대량생산 및 확보
• 환자 치료효능 모니터링
• 변이 대응 분석
목표
임상진입 후보물질 선제 확보
100/200일 이내 치료제 확보
치료제유효성평가


대비: 팬데믹 발생 전 신속개발 체계 구축
우선순위 감염병 선정
Virus Family
Arena
라싸
Bunya
SFTS
Corona
코로나19
MERS
Flavi
뎅기
Orthomyxo
인플루엔자
Paramyxo
니파
RSV
프로토타입 라이브러리 구축
우선순위병원체 또는 유사성이 높은 시제품
플랫폼 확보
핵심 플랫폼 국산화
치료제
기존 승인된 약물 사전 효능 확인 [약물 재창출]
광범위 효능 항바이러스제 & 항체치료물질 발굴
항바이러스제 대량신속 탐색기술
치료제 핵심기술 플랫폼 확립
◆ 우선순위 병원체 치료제(항체 · 항바이러스제 등) 개발 역량 및 인프라 강화, 국내외 공조를 통한 치료제 선제적 확보 (☞ 임상 1상 완료 목표)
목표 : 후보물질 발굴 → 임상1상 완료

대응: 팬데믹 발생시 신속 개발

100일 (Track 1) 타겟 병원체에 대한 임상1/2상정도의 안전성과 용량이 확인된 시제품 기 확보 시

200일 (Track 2) 타겟 병원체와 유사성이 높은 시제품 기 확보 시 (예시: SARS-CoV-3)

적합 플랫폼	구분	후보물질	비임상 생산	임상 1/2상 (1단계 초기 임상)	임상 3상 (2단계 임상 3상)	허가 및 심사 (3단계 임상 완료)
(치료제) 항바이러스제 항체치료제 등	T1(100일)	시제품 확보	30일 (대량생산)	생략	70일	
	T2(200일)	유사 시제품 확보	40일 (대량생산, 평가	60일 (임상1/2상 동시진행)	100일	
렉키로나주 개발	코로나19 (330일)	90일	120일	120일 (조건부허가)	-	

목표 : 100/200일 내 치료제 확보

평가 · 보완: 면역원성 및 치료임상 효능 평가 등

효능평가

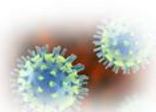
- ▶ 치료제 적용 후 임상효능평가
- ▶ 변이 발생 시 유효성 분석 등 사후평가

민간 지원

- ▶ 항바이러스제 약효평가 실험실 운영
- ▶ 약효평가거점실험실 확충

시설 · 자원

- ▶ 신종바이러스연구센터 (BL2/3)
- ▶ 국가병원체자원은행
- ▶ 질병청 BL4 시설활용 활성화



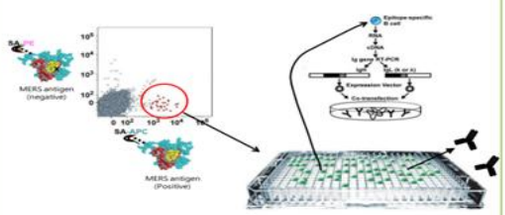


목표 : 치료제 효능에 대한 과학적·정책적 근거 마련

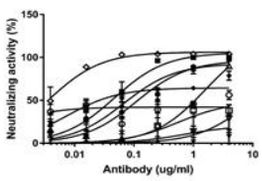
메르스 단클론 항체 개발 플랫폼 구축

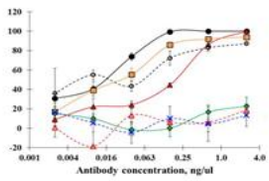
▶ 메르스 지속발생 및 재유입대비
→ 국가차원의 긴급대응 연구를
통한 사회적 불안감 해소

국내 메르스 회복 환자 PBMC로부터
MERS 특이항체 보유 B세포 분리 핵심 기술



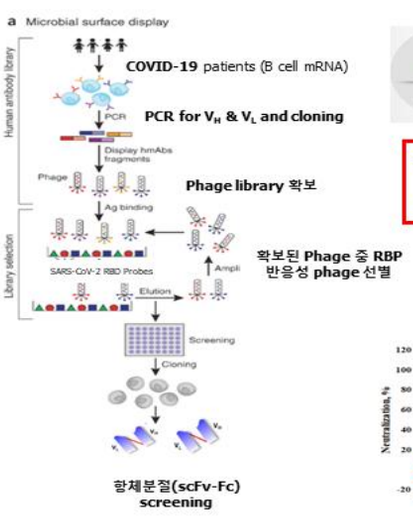
미국 NIH와 "정밀 의료와 메르스 치료제 개발 협력" 추진(2015-10-18)하에 핵심 기술 연수





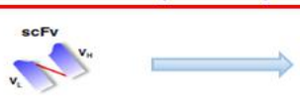
√ 메르스 항체 미국 NIH 공동 및 자체 개발
√ 단클론 항체 개발 플랫폼 구축

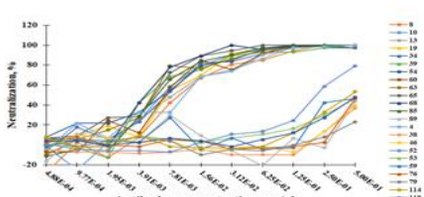
코로나19 항체치료제 후보물질 발굴

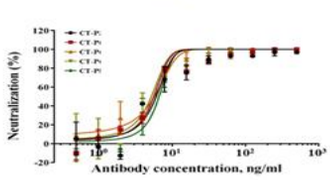


Int. J. Biol. Sci. 2020, J Biomedical Sci. 2020

수백 개의 항체분절(scFv-Fc) → 바이러스 중화능 평가 →
full IgG 후보 선별 → 생산성(동물세포) 고려 최종 후보 항체 선정





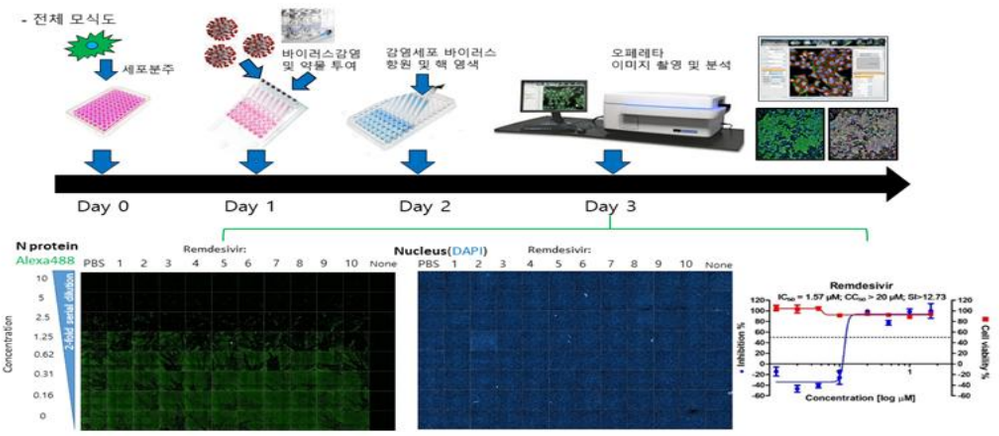


HTS 기반 치료제 신속 효능평가 플랫폼 확보

▶"Solidarity" WHO 주도 국제적 약물 재창출 임상시험 진행

▶"렘데시비르" 한·미·일 등에서 코로나19 치료제 최초 승인 [에볼라치료제]

☞ 신변종바이러스 대비 신속 대량 약물 선별법 구축 필요



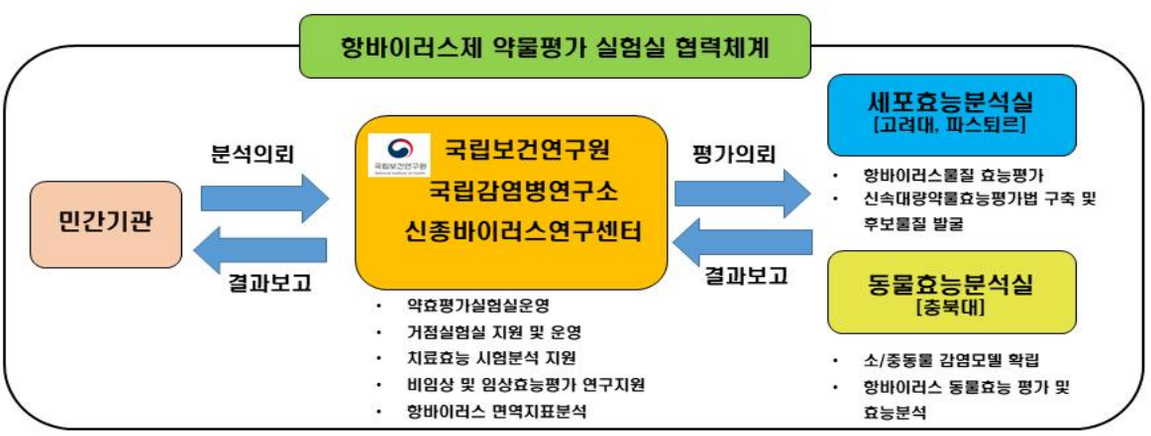
민관협력 항바이러스제 약효평가 거점실험실 구축

▶ 국가 공중보건 위기대응 연구역량 상시 강화

▶ 코로나19 등 바이러스 감염병 제어를 위한 치료제 후보물질 발굴 및 개발

▶ 약물의 항바이러스 효능 비임상(세포 및 동물) 평가 및 지원

▶ 항바이러스제 약물평가 거점실험실 지정·운영을 통한 협력 네트워크 구축



국내외 치료제 개발 네트워크 공조 강화

[국내]

SKRI 국가핵심 항체전문 연구소 스크립스코리아

연구협력의향서('22.4.)

감염완치자 항체라이브러리 개발

[국외]

한국화학연구원

연구협력의향서('22.11.)

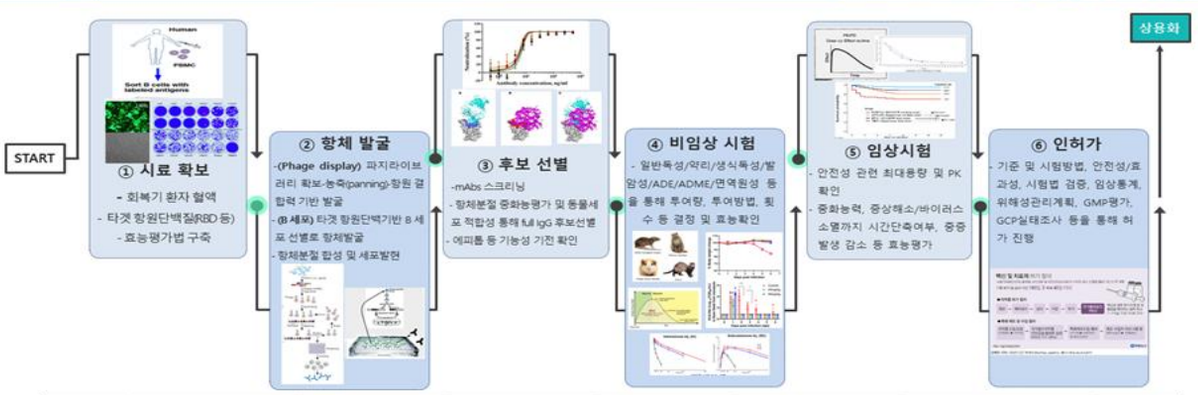
신변종 감염병 핵심기술개발

최신 기술 및 연구 자원확보를 통한 신변종 감염병 선제적 대응 연구역량 강화

국가	기관	내용	비고
미국	NIAID	SFTSV 항체치료제	수행 중('22~)
라이베리아	라이베리아감염병연구소	출혈열, 호흡기 바이러스 자원	수행 중('23~)
탄자니아	남동아프리카감염병연구소		
말레이시아	열대감염병연구 및 교육센터	SFTSV, 니파 연구자원 등	
호주	피터도허티	치료제 개발 기술 교류	진행 예정('24~)
남아공	국립전염병연구소	출혈열 바이러스 치료제 개발	수행 중('23~)
칠레/호주/독일	칠레-오스트랄 대학교, 퀸즈대학교, BNITM, RIZ, UKE	라싸열 바이러스 치료제 개발	수행 중('24~)

Korea National Institute of Infection Diseases / Novel Virus Research Institute

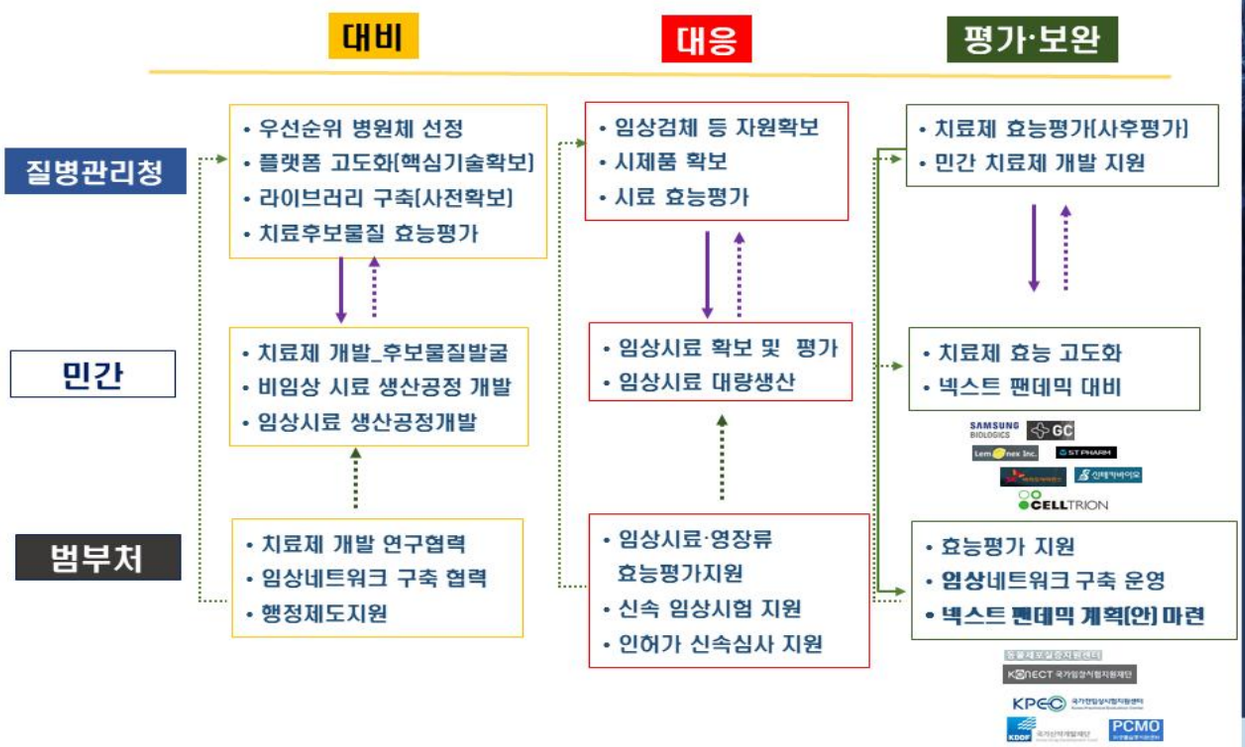
개발 단계별 역할 및 지원 - [예] 항체치료제 개발



개발 단계	시료 확보	항체발굴	후보항체 선별	비임상	시료생산 및 평가	임상	인허가
장애 요인	회복기 환자 혈액수집, 항원확보	항체 중화능 평가	후보항체 중화능 및 동물효능 검증	영장류 효능평가	비임상 및 임상시료 생산, 효능평가	임상환자 모집, 예산지원, 임상검체분석, 임상허가심사	신속 심사
주요 협력 기관	질병청/ 병원/ 기업/ 연구기관 복지부	질병청/ 연구기관/기업	질병청/ 연구기관/기업	과기부, 교육부 [국가전임상 지원센터]	질병청/ 기업 /산자부	질병청/ 기업/복지부/ 식약처/ 임상시험재단 검체분석기관	식약처

Korea National Institute of Infection Diseases / Novel Virus Research Institute

단계별 상호 역할 및 지원



고려사항

▶ 치료제 개발을 위한 전주기 민-관 협의체 구성 필요

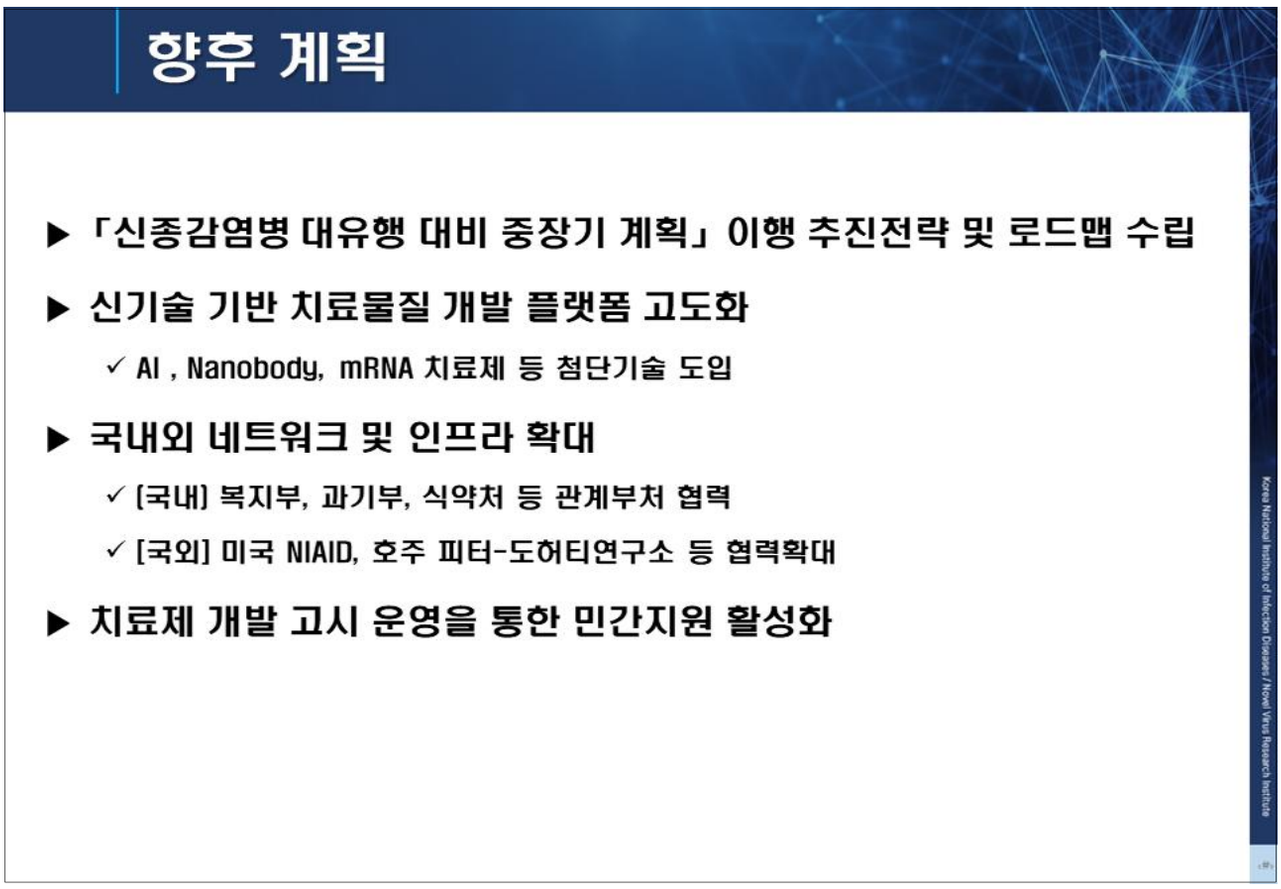
→ 평시/ 위기 시 상황에 따른 유연한 민관협력 체계 구축

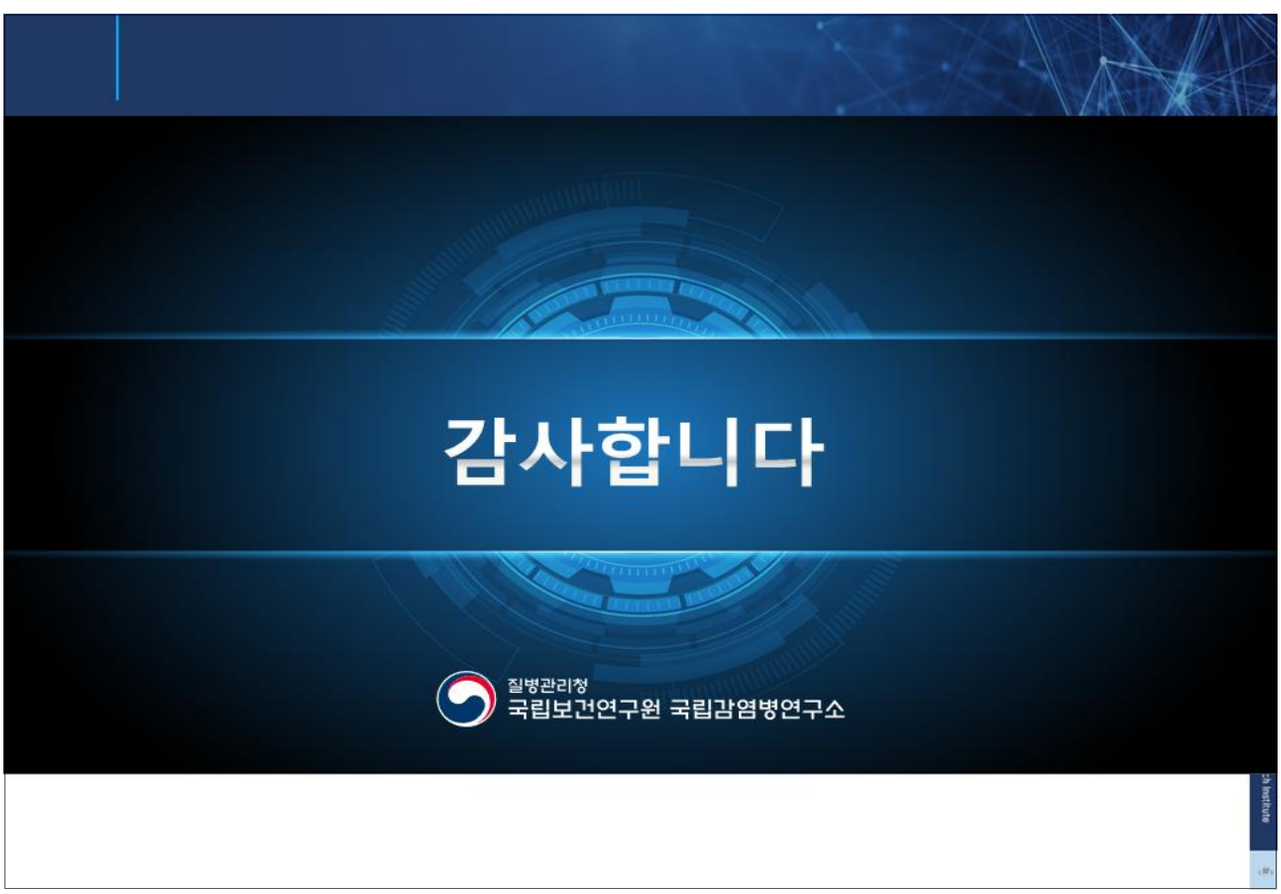
→ 치료제 개발을 위한 범정부 컨소시엄 혹은 사업단 마련

▶ 임상시험 관련 인허가 등 규제 간소화

▶ AI 활용 등 치료제 개발 데이타베이스 구축 및 운영

▶ 지속적 투자를 위한 출연금 등 신규 예산 확보 필요


향후 계획
▶ 「신종감염병 대유행 대비 중장기 계획」 이행 추진전략 및 로드맵 수립
▶ 신기술 기반 치료물질 개발 플랫폼 고도화
✓ AI , Nanobody, mRNA 치료제 등 첨단기술 도입
▶ 국내외 네트워크 및 인프라 확대
✓ [국내] 복지부, 과기부, 식약처 등 관계부처 협력
✓ [국외] 미국 NIAID, 호주 피터-도허티연구소 등 협력확대
▶ 치료제 개발 고시 운영을 통한 민간지원 활성화


감사합니다
질병관리청
국립보건연구원 국립감염병연구소

기조강연 2.

신종감염병 대유행 대비 100/200일 백신 개발전략 및 계획

2024
감염병연구기관 국제심포지엄
International Symposium for Infectious Diseases Research Institutes Cooperation

Keynote speech 2

Yoo-Kyoung Lee

- Korea Disease Control and Prevention Agency, National Institute of Health)
- Division Director

EDUCATION:

- 2004 D.V.M., Seoul National University School of Veterinary Medicine
- 1998 Master's Degree, Seoul National University School of Veterinary Medicine
- 1994 ABD(all but dissertation), Seoul National University School of Public Health

PROFESSIONAL EXPERIENCE:

- 2021 ~ Present Division Director, Korea Disease Control and Prevention Agency, Division of Vaccine Development Coordination
- 1998 ~ 2021 Senior Staff Scientist, Ministry of Food and Drug Safety

질병관리청
국립보건연구원

신종감염병 대유행 대비 100/200일 백신 개발전략 및 계획

2024. 3. 8.
공공백신개발지원센터

신종감염병 대유행 대비 중장기 계획('23.5.22)

백신개발전략 / 질병관리청 국립보건연구원

국가 백신 관련 정책('22)

- "윤석열 정부 120대 중점 과제"
  ▷ (포스트 코로나) 감염병 등 보건안보 관련 과제와 희귀난치 질환 등 국가적 해결 필요과제에 대한 **혁신적 연구개발 체계** 구축(한국형 Arpa-H)

	과제 목표	주요 내용
감염병 대응 체계 고도화	펜데믹 대비 과학적·근거기반 선진적 감염병 대응체계 구축	▪ 재유행 대비 백신 추가 접종 및 백신 이상 반응 국민 입증 부담 완화
바이오·디지털 헬스 글로벌 중심 국가 도약	보건안보전략기술 집중 투자와 글로벌 협력 강화로 백신·치료제 강국 도약	▪ 혁신적 연구개발 체계 구축 -'초고속 백신·치료제 개발 전략'
예방적 건강관리 강화	국가예방접종 지원 백신 및 대상 확대로 예방 가능한 감염병 대비	▪ 국가 필수 예방 접종 확대 및 백신 안전관리 체계 구축

- 범정부 차원의 감염병 위기 대응 상황 대비를 위한 중장기 계획 수립
  ✓ 제3차 국가 감염병 위기대응 기술개발 추진 전략('22~'26)

백신 국산화 기술 확보	2021년 50%	→	2026년 70%
	국가 예방 접종		피내용 BCG
			성인용 디프테리아-파상풍-백일해(TdaP)
			디프테리아-파상풍-백일해(DTaP)
			자궁경부암(HPV)
	기타 예방 접종		소아장염(Rotavirus)
			수막구균성 수막염(MCV)
	대유행, 대테러 대비		탄저

[신종감염병 대유행 대비 중장기계획 10대 핵심과제]

감시·예방	① 감염병 조기경보를 위한 통합 감시체계 구축
	② 글로벌 보건안보 선도 및 국제협력체계 강화
대비·대응	③ 세계에서 인정받은 초기 대응역량 지속 발전
	④ 日 확진자 100만명 대응가능한 의료체계 구축
	⑤ 대규모&장기 유행에 흔들리지 않는 필수인력 확보
	⑥ 감염에 취약한 시설·집단을 안전하게 보호
기반	⑦ 협력적·효율적 위기대응 위한 튼튼한 기반 조성
	⑧ 고도화된 정보시스템 및 빅데이터 플랫폼 구축
회복	⑨ 피해완화와 조기 회복을 위한 두터운 지원체계
연구개발	⑩ 백신·치료제 개발 가속화를 위한 R&D 지원체계를 혁신

- 신종감염병 대유행 대비 백신개발 전략

2024년 질병관리청 주요 정책계획 ('24.2.19)

백신개발전략 / 질병관리청 국립보건연구원

2024년 주요 정책계획

2024. 2.

질병관리청

2 업무 추진 방향

2024 비전: 새로운 위기에는 신속하게 일상속 위험에는 탄탄하게

정책목표: 보건안보 강국, 건강사회 실현을 위한
- 하루 100만명 감염병 환자 대응 전략 마련
- 대유행 100·200일 내 백신·치료제 신속개발 기반 구축
- 100세 시대 생애주기별 건강한 일상 보호

핵심과제

1. 새로운 감염병 유행에 대한 선제적 대비·대응	① 촘촘한 감시, 정밀한 위기예측 ② 신속한 진단, 고도화된 역학조사 ③ 빅데이터 기반 방역, 탄력적 의료대응 ④ 팬데믹 대비체계 마련
2. 상시 감염병 위험요인 관리 및 퇴치	① 국가예방접종 확대 및 운영 고도화 ② 감염병 전파의 잠재 위협요인 관리 ③ 검진·예방 강화로 주요 감염병 퇴치 ④ 의료관련 감염 및 항생제 내성 관리기반 강화
3. 초고령사회 질병 대비 및 건강취약계층 보호	① 지역사회 만성질환 예방·관리 강화 ② 지속가능한 생애주기 건강조사체계 ③ 거주지 중심 두터운 희귀질환자 지원 ④ 손상·건강위해 예방 안전망 공고화
4. 국가 보건의료 연구역량 제고	① 백신·치료제 신속개발 및 지원체계 강화 ② 건강격차 해소를 위한 만성질환 연구 ③ 보건의료 연구 데이터 확보·개방
5. 공중보건 글로벌 협력 선도	① 글로벌 보건안보 역량·네트워크 강화 ② 공중보건 정책 및 기술 연계 강화

4 국가 보건의료 연구역량 제고

◈ 신종감염병 대유행 시 백신·치료제를 신속 개발할 수 있는 기반을 만들겠습니다.
◈ 국내·외 연구 협력으로 미해결 감염병, 만성질환을 극복하겠습니다.

1 신종감염병 대비 백신·치료제 신속개발 및 지원체계 강화

□ (백신) **국가 백신 R&D 핵심기관**으로서, 국내·외 및 민·관과 전략적 연계·협력으로 백신 **선제 개발 및 국산화로 백신주권 확보**

○ **(전략)** 신종감염병 대유행 위기 시 **신속한 백신 개발**을 위해 **우선순위 병원체**(9종*) 중심 **투트랙 전략** 추진(제제개발, 글로벌 공조)

* 코로나19, 신종인플루엔자, 니파, 라싸, 웨기, SFTS, 지큰구니아, 신종출근유행상출혈열(한탄), RSV

○ **(국산화) 생물데리** 등 **공공인프 감염병 백산*** 개발, mRNA **핵심기술 확보**** 등 국가 주도의 백신 개발로 **보건안보 강화**

* 탄저백신 공동개발(식약처 품목허가 진행중) ** 백신전달체(LNP등), 항원발현 벡터(IVT) 기술

○ **(인프라)** **"국가첨단백신개발센터" 운영**으로 안공지능 활용 백신 항원 설계, 디지털(in-silico) 비임상, 백신 항원 라이브러리 등 **인프라 구축**

신종감염병 백신 개발 전략

백신개발전략 / 질병관리청 국립보건연구원

(팬데믹 발생전) 체계 구축 → (팬데믹 발생시) 100/200일이내 신속 개발 추진

'대비 단계: 팬데믹 발생전 신속개발 체계 구축'이 필수적

1단계 : 대비(최대한 준비)

(1단계) 대비 : 팬데믹 발생 전 신속 개발 체계 구축

01 우선순위 감염병 선정	02 핵심 신기술 확보	03 백신 라이브러리 구축	04 미해결/공공안보 백신 선도 개발
• 우선순위 선정 병원체 파악 • 우선순위 연구 및 비축 대상 병원체 9종 선정	• mRNA백신 개발(단기) • mRNA 국내 자체 기술개발(장기) • 신기술(면역증강제, 항원설계) 국산화	• 시제품 사전 확보 • 시험용 프로토타입(시제품) 생산 및 백신라이브러리에 비축 • 국가첨단백신개발센터 설립	• 위험도 높은 차세대 결핵 백신 개발 • 3세대 두창, 아데노55형, 탄저 등 공공안보 백신 개발

1단계: 우선순위 백신 개발 계획

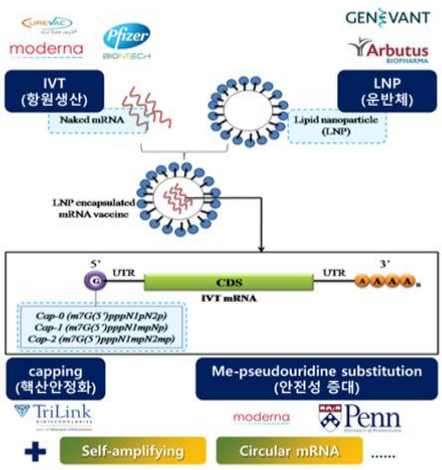
- ☑ 우선순위 병원체(9종) 중심으로 단계적 개발
- ☑ (two-track 전략) 국내 자체개발, 글로벌 개발 공조

개발전략

전략	병원체	현 개발단계 (국내)	실용화 목표
국내 자체 개발	신종인플루엔자	비임상	품목허가
	코로나19	임상1상	품목허가
	RSV	비임상	품목허가
	SFTS	비임상	품목허가
	신증후군출혈열(한탄)	후보물질 개발	품목허가
글로벌 공조	라싸	비임상	임상1상
	니파	후보물질 개발	임상1상
	뎅기	비임상	임상1상
	치쿤구니아	후보물질 개발	임상1상

1단계; mRNA 백신 플랫폼 등 핵심기술 확보

mRNA 백신 플랫폼 핵심기술요소



개발 현황

- 일부기술 도입을 통한 mRNA 백신신속 개발 추진 중
- mRNA 백신 후보물질 질병청 자체 연구개발 중
  * 차세대 결핵, SFTS, 일본뇌염, 다가형코로나 및 엠폭스
- 산·학·연 대상 핵심기술개발 및 (비)임상 시험 연구과제 지원
  * 신변종감염병 mRNA백신 사업단(질병청/복지부): 팬코로나, 지카, 라싸열 등

향후 계획

- 특허회피 가능 mRNA백신 핵심요소 기술 개발 지속 지원
  * 생산벡터, 고효능 원형 mRNA 벡터, LNP대량 생산 및 개선 등
- 한국형 mRNA백신 플랫폼 구축('28~30)
  * 특허회피 가능 mRNA 백신기술 고도화를 통한 한국형 플랫폼 구축

1단계; 백신 라이브러리 구축

국가첨단백신개발센터 사업내용

(재)국가첨단백신개발센터 사업 내용

	STEP 1.	STEP 2.	STEP 3.	STEP 4.
주요 기능	AI기반 항원 디자인	백신 플랫폼 확보 및 소규모 생산	신속 검증 시스템 구축	항원 라이브러리 구축 및 운영
	AI 기술기반 후보물질 발굴	소규모 비임상검체 생산·분석 지원	(비)임상데이터 분석	항원 라이브러리 생산·비축
주요 역할	AI 기술을 활용하여 후보물질 발굴	백신 후보물질 선정 및 검증을 위한 소규모 생산 (mRNA & DNA 활용)	생물안전연구시설 등을 통한 검증	검증이 완료되어 차후 빠르게 백신으로 개발될 수 있는 항원 비축
센터 정의	AI 기술 기반 항원 물질을 발굴 및 디자인하여 신속하게 테스트하고 백신 시제품을 비축할 수 있는 시설			
백신 라이브러리	우선순위 병원체 대상으로 비임상·임상 1-2상 수행하여 백신(시제품) 라이브러리를 구축 → 위기시, 백신 시제품과 백신 제조에 필요한 데이터를 제공하여 100/200일내 백신개발			

위치 및 사업기간	• 위치 : 경북 안동시 경북바이오산업단지 일원 • 사업기간 : '23년 ~ '27년 (5년)
규모	• 부지 약 10,000㎡, 건축 약 5,000㎡(연구시설, 1개동)
총사업비	• 총 사업비(1단계) : 95억 원(국비[건축비, AI·빅데이터구축비]) + 95억 원(지방비[부지·연구장비]) • 예산확보: '23년 10억, '24년 22억

2단계: 대응 (즉각적반응)

백신개발전략 / 질병관리청 국립보건연구원

(2단계) 대응 : 팬데믹 발생 시 신속 개발 추진

01 다기관 협력

- 다기관 참여 (비)임상시험 등 총력 지원
- 복지부임상, 과기부비임상, 산업부생산, 식약처허가지원 등

02 임상 네트워크 강화

- 병원, 연구기관, 국제기구 등과 협력하여 국내외 임상연구 등 실시하여 기간 단축 추진

03 긴급 대응 매뉴얼 수립

- 감염병 위기 단계별로 현장 중심의 신속 체계 가동 매뉴얼 마련
- 감염병 연구기관 협의체 중심의 R&D 위기대응 단계별(예측, 진단, 치료제 및 백신 등) 과기부 기초·기전 분야 위기대응 매뉴얼(모의훈련 등) 연계
- 산학연관 임무중심의 시료확보-비임상-임상진입-허가 긴급 대응 및 협력

04 감염병임상연구센터 마련

- 임상시험 네트워크, 효능평가, 표준물질 지원 등 신속 임상연구 전담조직 등 체계 마련
- 국립감염병연구소 분소 및 조직 신설 추진

2단계: 대응 (즉각적 반응)

백신개발전략 / 질병관리청 국립보건연구원

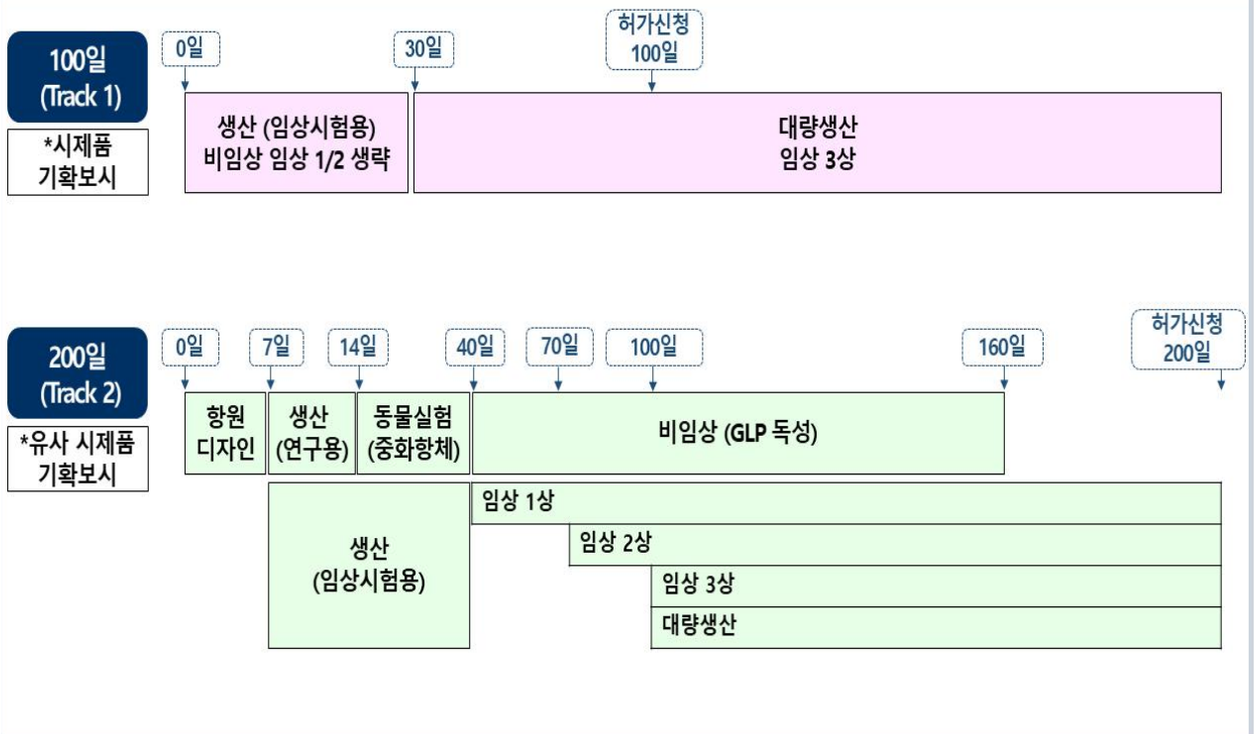
개발 Track	초기 임상: 비임상, 1/2상 시료 제조	임상 1/2상 임상 3상 시료 제조	임상 3상 대량 생산	허가 및 심사	개발 일정	적합 플랫폼
1	30일	생략 (시제품 기 확보시)	70일		100일	mRNA
2	40일	60일	100일		200일	mRNA

100일 (Track 1) [임상 1/2상] 해당 수준의 안전성과 용량 데이터가 확보된 타겟 병원체 프로토타입 활용 가능 시 생략

200일 (Track 2) 임상 1/2상 단계에서 타겟 병원체와 유사성이 높은 프로토타입을 미리 확보한 경우 수행 가능 (예: SARS-CoV-3 프로토타입)

2단계(대응): 100/200일 개발 일정 시나리오(안)

백신개발전략 / 질병관리청 국립보건연구원



3단계: 평가·보완

백신개발전략 / 질병관리청 국립보건연구원

(3단계) 대응 : 팬데믹 발생 후 평가·보완

01 면역원성 효능평가

- 백신 적용 후 임상효능평가
- 변이 발생 시 면역원성 분석 등 사후평가
- 백신 접종자 코호트 기반 장기 추적조사 실시 및 정책 반영

02 민간지원

- 비임상시험 네트워크 운영
- 임상시험 및 임상시험검체분석기관(GCLP) 네트워크 운영

03 시설·자원

- 공공백신개발지원센터(BL2, BL3)
- 국가병원체자원은행
- 질병청 BL4 시설활용 활성화

단계별 역할 및 지원

백신개발전략 / 질병관리청 국립보건연구원

	1단계: 대비	2단계: 대응	3단계: 평가·보완
질병관리청	• 우선순위 병원체 선정 • 핵심신기술 확보 • 백신 라이브러리 구축(시제품 확보 등)	• 다기관 참여 (비)임상시험 등 총괄 • 임상시험네트워크, 효능평가, 표준물질 등 신속 임상연구 지원	• 면역원성 효능평가 • 백신연구개발 시설 (BL3/4) 및 효능평가 민간지원 • 변이주 등 병원체 분리 확보, 분양
기업	• 후보물질 생산 공정 개발 • 시제품생산	• (비)임상시험(GLP 등) 생산 등 신속개발	• 임상 IND 신청 및 관리
범부처	• 전주기 개발 협력 • 국내외 임상네트워크 구축	• 다기관 참여 (비)임상시험 지원 • 비임상 및 임상네트워크 협력	• 해외임상시험 실시 • 비임상 및 임상네트워크 협력

대한민국정부 KPEC K-VCAST 재단법인 백신안전기술지원센터 International Vaccine Institute CEPI

질병청(공공백신개발지원센터) 주요 역할

공공백신개발 지원센터소개 / 질병관리청 국립보건연구원

백신 효능평가를 위한 평가법 확립 및 시험·분석 지원

국가 정책 수립	후보물질 발굴단계(Discovery)		백신개발단계(Development)		수출(Export)
백신개발 로드맵	유효물질 발굴	선도물질 도출	비임상	임상	품목허가	PQ지원
Priority	Target	Candidate	민간 지원 단계		Vaccine	

국내협력

- 백신실용화기술개발사업단
- mRNA백신사업단
- 글로벌백신선도사업단
- 산·학·연·관

국제협력

NIH National Institute of Allergy and Infectious Diseases moderna International Vaccine Institute CEPI

질병청(공공백신개발지원센터) 국산 백신 개발 역량

백신개발현황 및 성과 / 질병관리청 국립보건연구원

코로나19 백신개발

SKB 허가/국내 접종(22년), WHO PQ인증(23년)

mRNA 코로나19 백신 임상(2개) 진입 성과

* 신변종 mRNA백신사업단 지원(아이진, 에스티팜)

(비)임상검체 분석 지원

플랫폼	기업	백신	비임상	임상 1상	임상 2상	임상 3상	비고
합성항원	SK바이오 사이언스	GBP510-AS03		80	240	9,962	3상
DNA	진원생명과학	GLS-5310		45	126		1/2a상
RNA	큐라티스	QTP104 (repRNA)		36			1상
RNA	에스티팜	STP2104 (mRNA)		30			1상

질병청 개발 백신

백신	플랫폼	진행현황	향후계획
차세대결핵	재조합	마우스모델에서 효능평가	비임상 연구추진 ('24~)
아데노 55형	불활화	생산공정 개발 및 비임상 (독성 및 효력) 수행 중	영장류 효능평가 (~'24) 및 임상연구 추진('25~)
3세대 두창	약독화	생산공정 확립 및 비임상(독성 및 약리) 수행 중	임상시험 추진('24~)
탄저	재조합	비임상 및 임상 완료	품목허가신청 ('23.10월)

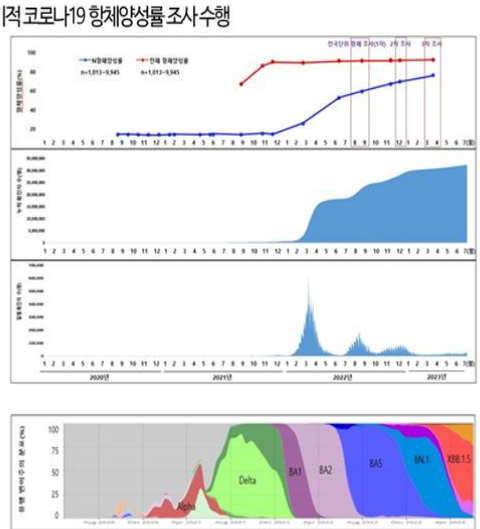
질병청(공공백신개발지원센터)의 과학적 근거 제공

코로나19 백신개발현황 및 성과 / 질병관리청 국립보건연구원

코로나19 항체양성률 조사

신종 및 법정 감염병 돌발 유행에 대비하여 감염취약집단 확인 및 유행위험 평가를 위해 전국단위 혈청역학 감시체계 구축·운영

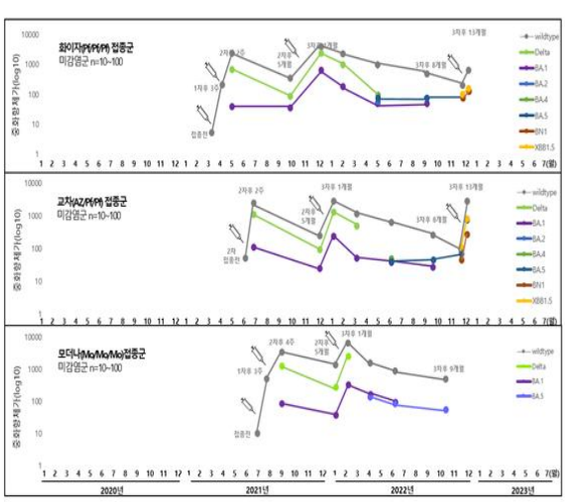
- 대표성 강한 국가 통계 산출을 위한 지역 대표 표본 1만명(만 5세 이상)에 대한 주기적 코로나19 항체양성률 조사 수행



백신 면역원성 장기 추적조사

국내 도입 백신 접종자의 면역원성 장기 추적조사를 위한 코호트 구축 및 운영

- 국내 도입 코로나19 백신 5종 및 2가 백신 접종자에 대한 코호트 구축 후 주기적 검체 수집 및 중화항체 분석 실시



향후 계획

- 신속 백신개발을 위한 mRNA 등 핵심기술 및 플랫폼 고도화
  → AI(인공지능) 기반 백신 후보물질 발굴 등 첨단기술 도입, 백신 라이브러리 구축 등

- 국내·외 연구협력 네트워크 확대
  - (국내) 백신안전기술센터(식약처 재단법인)
    국가전임상기술센터(과기부 출연연)
  - (국외) 국제백신연구소(IVI),WHO, CEPI 등 백신 공동연구

- 고시 제정('24.1월), BL3/4 시설, 병원체자원은행 활성화을 통한 민간지원 사업 활성화

세션 1.

신종감염병 특성 및 임상연구

Chair

Man-Seong Park

- Department of Microbiology, Institute of Viral Disease, College of Medicine, Korea University
- Professor

EDUCATION:

- 1999 Korea University Graduate School, Ph.D.
- 1996 Korea University Graduate School, M.S.
- 1994 Korea University, College of Science, B.S.

PROFESSIONAL EXPERIENCE:

- 2022 ~ Present Member, Committee for Infectious diseases, PRESIDENTIAL ADVISORY COUNCIL ON SCIENCE & TECHNOLOGY,
- 2007 ~ 2014 Assistant/Associate Professor, Dept of Microbiology, College of Medicine, Hallym University
- 2014 ~ Present Assistant/Associate Professor, Dept of Microbiology, College of Medicine, Korea University
- 2005 ~ 2007 Instructor, Dept of Microbiology, Icahn School of Medicine at Mount Sinai, USA
- 1999 ~ 2004 Post-doctoral fellow, Dept of Microbiology, Icahn School of Medicine at Mount Sinai, USA
- 2022 ~ Present Board member, Government-wide R&D Fund for Infectious Disease Research (GFID), Korea

01

SFTSV 감염 연령에 따른 병인 기전

최영기 소장
한국바이러스기초연구소

Speaker

Young-Ki Choi

- Korea Virus Research Institute, IBS
- Managing Director

EDUCATION:

- 2002 Ph.D, University of Minnesota, Colege of Veterinary Medicine (USA)
- 1999 MS, Chungnam National University, College of Verterinalry medicine
- 1996 DVM, Chungnam National University, College of Verterinalry medicine

PROFESSIONAL EXPERIENCE:

- 2021 ~ Present Managing Director, Korea Virus Rsearch Instiitue, IBS (Korea)
- 2023 ~ 2024 Chungbuk National University, College Medicine,
  (Assistant professor - Professor)
- 2023 ~ 2024 Post-Doc Fellow, St. Jude Children's Research Hospital (USA)

Topic

Age-depedent differential pathogenesis of SFTSV infections

Abstract

Dabie bandavirus (severe fever with thrombocytopenia syndrome virus [SFTSV]) induces an immunopathogenic disease with a high fatality rate; however, the mechanisms underlying its clinical manifestations are largely unknown. In this study, we applied targeted proteomics and single-cell transcriptomics to examine the differential immune landscape in SFTS patient blood. Serum immunoprofiling identified low-risk and high-risk clusters of SFTS patients based on inflammatory cytokine levels, which corresponded to disease severity. Single-cell transcriptomic analysis of SFTS patient peripheral blood mononuclear cells (PBMCs) at different infection stages showed pronounced expansion of B cells with alterations in B-cell subsets in fatal cases. Furthermore, plasma cells in which the interferon (IFN) pathway is downregulated were identified as the primary reservoir of SFTSV replication. This study identified not only the molecular signatures of serum inflammatory cytokines and B-cell lineage populations in SFTSV-induced fatalities but also plasma cells as the viral reservoir. Thus, this suggests that altered B-cell function is linked to lethality in SFTSV infections.

02

마우스 모델에서의 인간 인플루엔자 A바이러스 헤마글루틴의 탈당쇄화에 따른 병원성 증가

최장훈 연구관
국립감염병연구소 급성바이러스연구과

Speaker

Jang-Hoon Choi

- Divison of Acute Viral Disease Research, Center for Emerging Virus Research, Korea National Institute of Health
- Deputy Scientific Director

EDUCATION:

- 2011 Hanyang University Graduate School, Ph.D.
- 2004 Korea University graduate School, M.S.
- 2001 Hanyang University College of Science, B.S.

PROFESSIONAL EXPERIENCE:

- 2020 ~ Present Deputy Scientific Director, Division of Acute Viral Disease Research, Center for Emerging Virus Research, National Institute of Infectious Diseases, KNIH
- 2016 ~ 2020 Staff Scientist, Division of Viral Disease Research, Center for Infectious Diseases, KNIH
- 2016 ~ 2016 Visiting scientist, VRC, NIAID, NIH
- 2014 ~ 2016 Visiting fellow, NIAID, NIH
- 2007 ~ 2014 Staff Scientist, Div. of Influenza virus, Center for Infectious Diseases, Korea National Institute of Health

Topic

Deglycosylation of seasonal influenza virus (A/H3N2) hemagglutinine confers infectivity and pathogenicity during mouse adaptation

Abstract

Pandemic Influenza A viruses (IAVs) occasionally cross the species barrier through either host adaptation or genetic reassortment. Understanding the viral genetics that underlie virulence and cross-species transmission is critical for designing durable vaccines and therapeutics. In our previous work, we successfully established a mouse adapted strain (maSW293) from seasonal influenza A/H3N2 virus (A/Switzerland/9715293/2013). Unlike the parental strain, maSW293 exhibits infectivity and pathogenicity in mice. Pathogenicity analysis using recombinant viruses revealed that hemagglutinin (HA) plays a pivotal role in infection and mortality in mice. Notably, three identified mutations (N160D, T183A, N262T) within the HA sequence have the potential to induce deglycosylation in the globular head domain.

The analysis of mouse pathogenicity using recombinant viruses revealed the significant contribution of HA mutations to both infection and mortality in mice. Each virus carrying the deglycosylation mutation exhibited infectivity in mice. Notably, mice infected with the triple mutant virus exhibited a significantly reduced survival rate compared to the wild-type virus. Consequently, infection with the mutant viruses led to severe lung pathology and elevated induction of inflammatory cytokine and chemokine. Interestingly, the triple mutant virus exhibited not only enhanced α-2,6pism. Additionally, mutant viruses carrying the T183A and N262T mutations showed reduced NA activity, suggesting a potential contribution to viral fitness during host adaptation.

Collectively, the finding from this study suggest that the deglycosylation of the globular head of the HA can enhance pathogenicity and facilitate cross-species adaptability in mice. This is likely achieved through alterations in receptor binding affinity and NA activity.

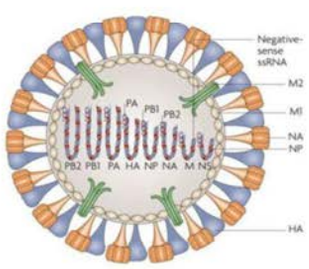
International Symposium for Infectious Diseases Research Institutes Cooperation [IDRIC]
2024. 3. 8.

Deglycosylation of human influenza A virus (H3N2) hemagglutinin increases virulence in mice

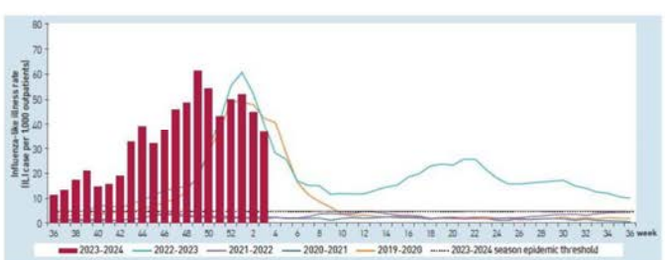
Jang-Hoon Choi
Center for Emerging Virus Research, National Institute of Infectious Diseases,
Korea National Institute of Health

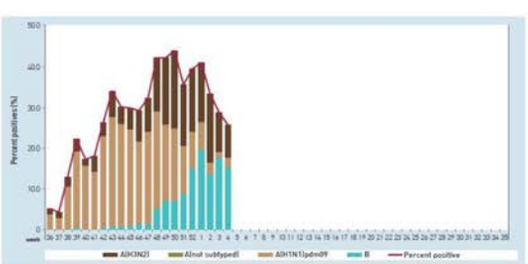
2024 IDRIC

Influenza virus



- ***Orthomyxoviridae*** **family**
- **(-)ssRNA virus, 8 segmented RNA**
- **Current seasonal influenza viruses: A(H3N2, H1N1), B(Vic/Yam)**
- **Infects up to 20% of the population each year**



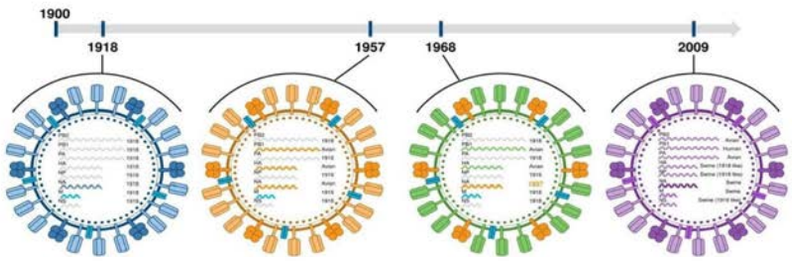


PHWR, KDCA, Feb, 2024

National Institute of Health
Republic of Korea

2024 IDRIC

Pandemic Influenza viruses



H1N1	H2N2	H3N2	H1N1
1918: "Spanish Flu"	**1957: "Asian Flu"**	**1968: "HongKong Flu"**	**2009: "Swine Flu"**
A(H1N1)	A(H2N2)	A(H3N2)	A(H1N1)
50 -100 M deaths	1-4 M deaths	1-4 M deaths	0.1-0.5 M deaths

Credit: US National Museum of Health and Medicine

Walter N. Harrington et al., *EMM*, 2021

National Institute of Health
Republic of Korea

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Risk Assessment Tools

IRAT (CDC, 2011)

Virus	• **Genomic variation** • **Receptor binding** • **Transmission in lab animals** • **Antivirals and treatment options**
Population	• Existing population immunity • Disease severity and pathogenicity • Antigenic relationship to vaccine candidates
Ecology	• Global geographic distribution • Infections in animals • Human infections and transmission

TIPRA (WHO, 2016)

Virology	• **Genomic characteristics** • **Receptor binding properties** • **Transmission in animal model** • **Susceptibility to antiviral treatment**
Public Health	• Population immunity • Disease severity • Human infection
Animal Health	• Geographic distribution in animals • Infections in animals

IRAT: Influenza Risk Assessment Tool
TIPRA: Tool for Influenza Pandemic Risk Assessment

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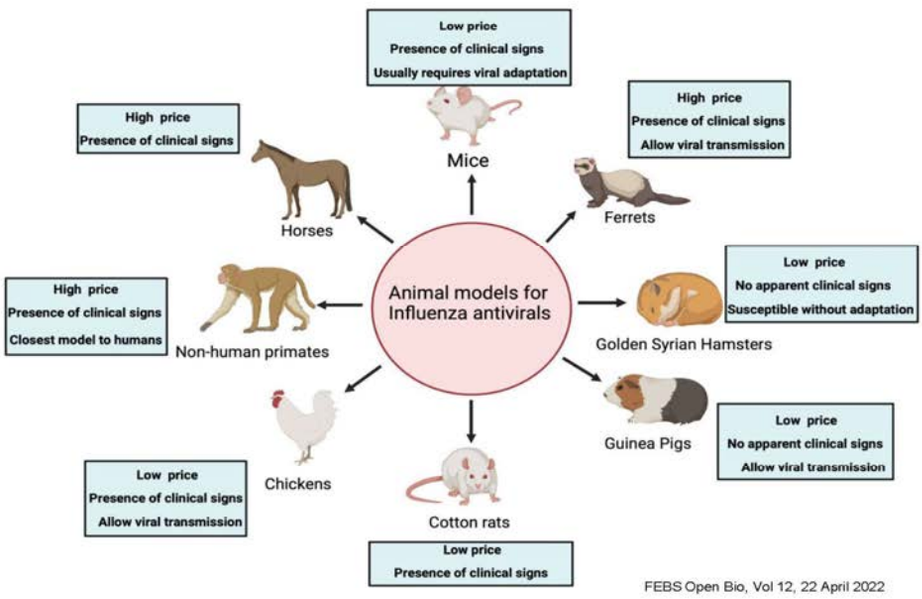
Animal models for influenza study



FEBS Open Bio, Vol 12, 22 April 2022

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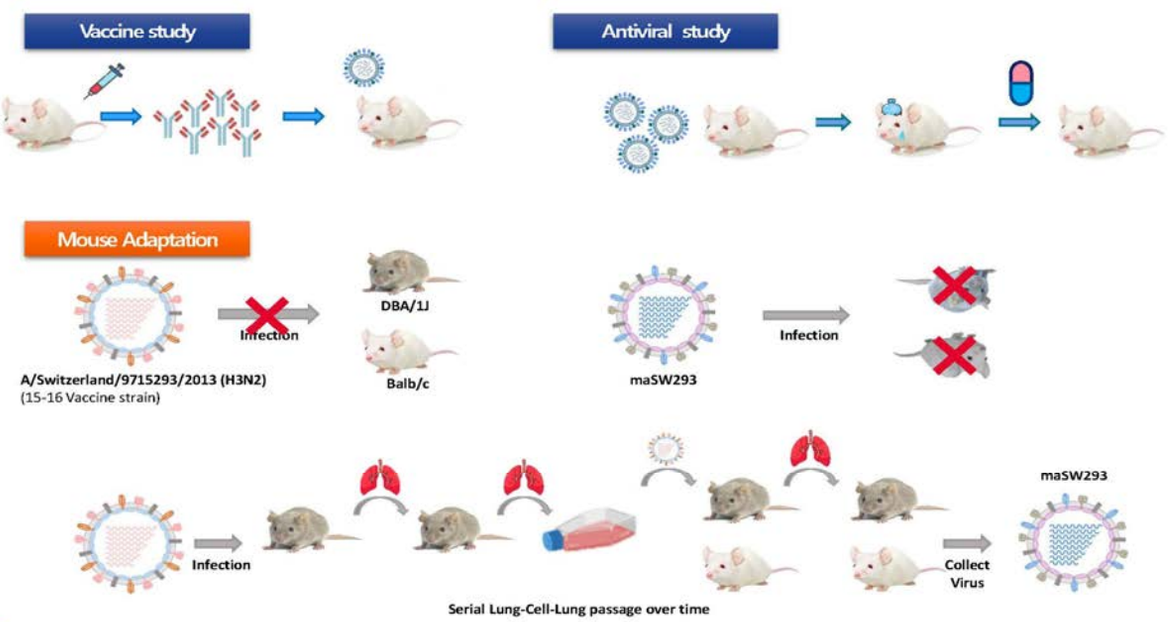
Experimental mouse adaptation



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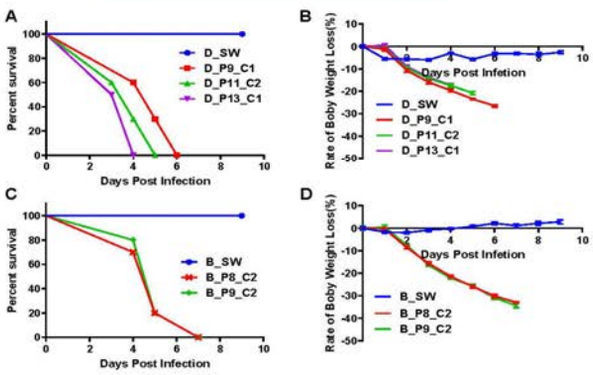
Generation of mouse adapted(MA) H3N2 virus

Virulence of H3N2 MA strains



Amino acid substitutions idendified in H3N2 MA strains

Name	HA							NA			NP			PA				PB2	
	18	144	160	183	209	262	522	331	369	463	34	189	384	86	356	421	609	713	323	355
A/Switzerland/9715293/2013	K	A	N	T	F	N	E	S	T	D	D	M	G	M	E	V	K	Y	F	R
DBA/1J_P9_C1	K	T	N	A	S	T	D	S	M	D	D	M	G	M	E	V	K	Y	L	R
DBA/1J_P11_C2	K	T	N	A	S	T	E	S	A	N	D	M	R	I	E	V	R	H	L	R
DBA/1J_P13_C1	K	T	N	A	S	T	E	S	K	D	D	I	R	I	E	V	R	H	L	K
Balb/c_P8_C2	Q	T	D	A	S	T	E	R	T	D	N	M	G	I	E	F	R	H	L	R
Balb/c_P9_C2	Q	T	D	A	S	T	E	R	T	D	N	M	G	I	K	F	R	H	L	R

National Institute of Health
Republic of Korea

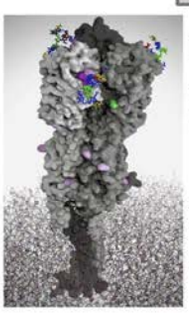
Choi et al., *PLOS ONE*, 2020

2024 IDRIC

Amino acid substitutions of maH3N2 virus

PB2	PA	HA	NA	NP
F323L	M86I, V421F, K609R, Y713H	K18Q, A144T, N160D, T183A, F209S, N262T	S331R	D34N

HA mutation



Hemagglutinin glycosylation

1) HA Immunogenicity

Escape Humoral Immunity (Abs Shielding)

Protein folding

2) Viral Virulence

Receptor binding

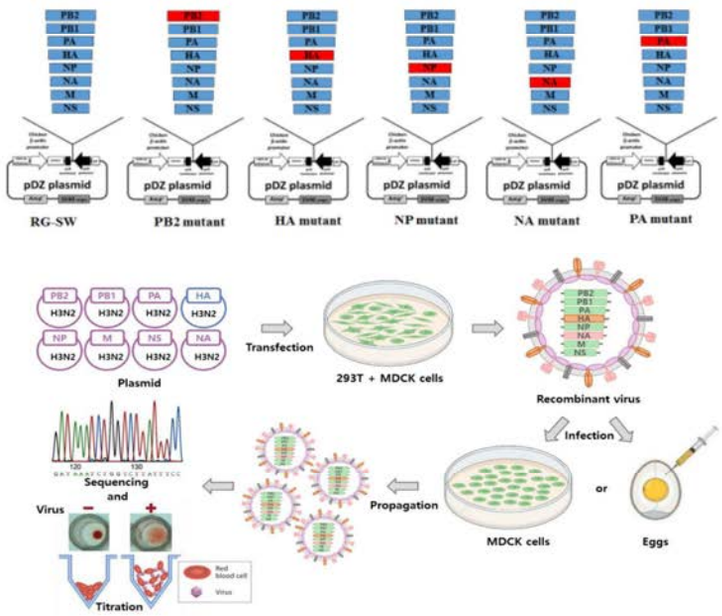
Avoid Innate immune response (C-type Lectin)

National Institute of Health
Republic of Korea

Altman et al., *host-Microbe Biology*, 2019

2024 IDRIC

Generation of mutant viruses (Reverse-Genetics)



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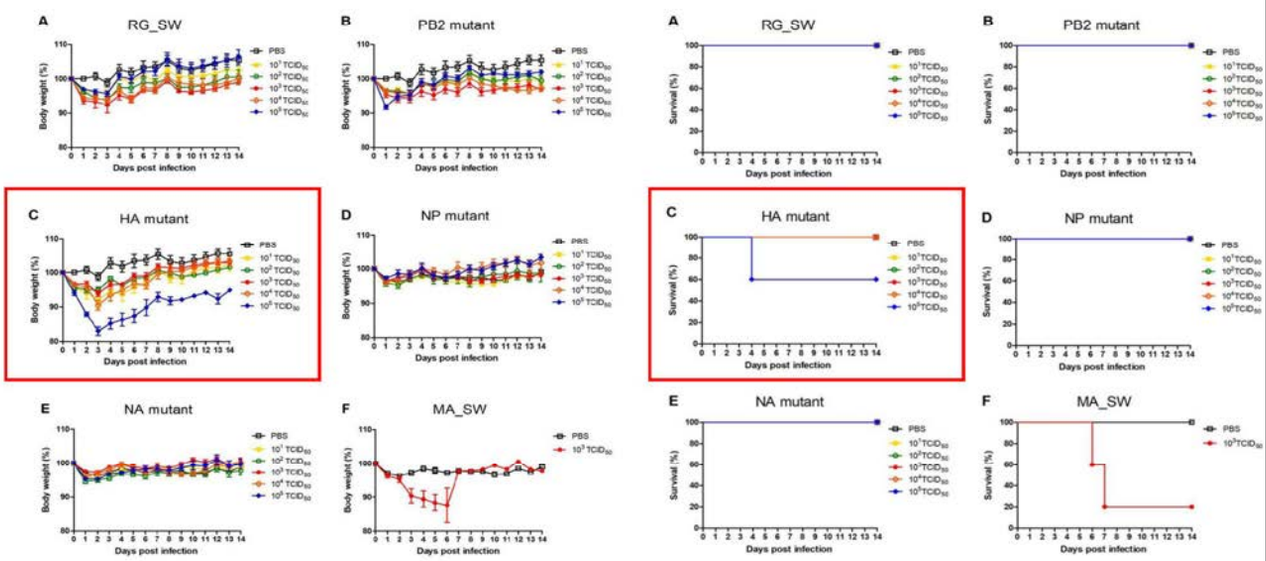
Republic of Korea

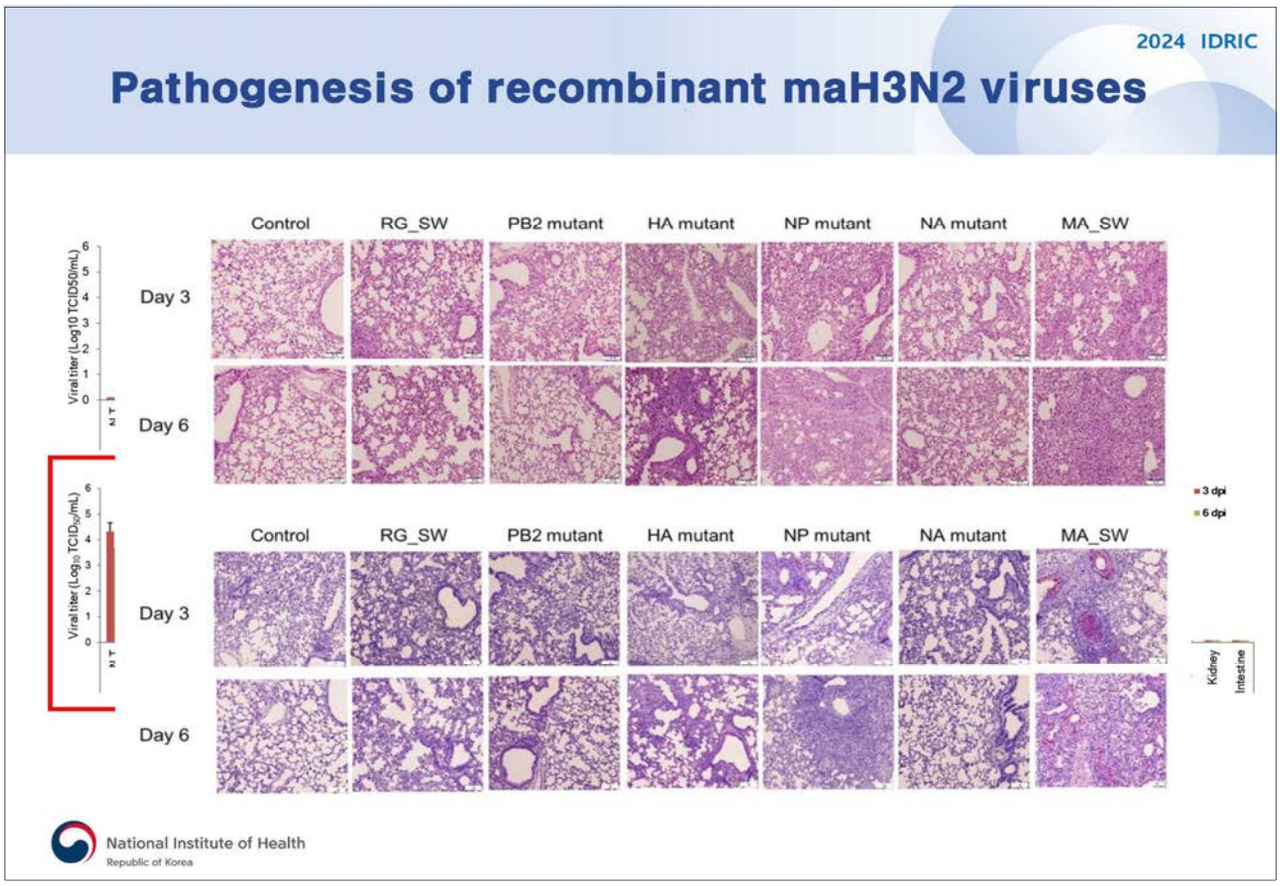
2024 IDRIC

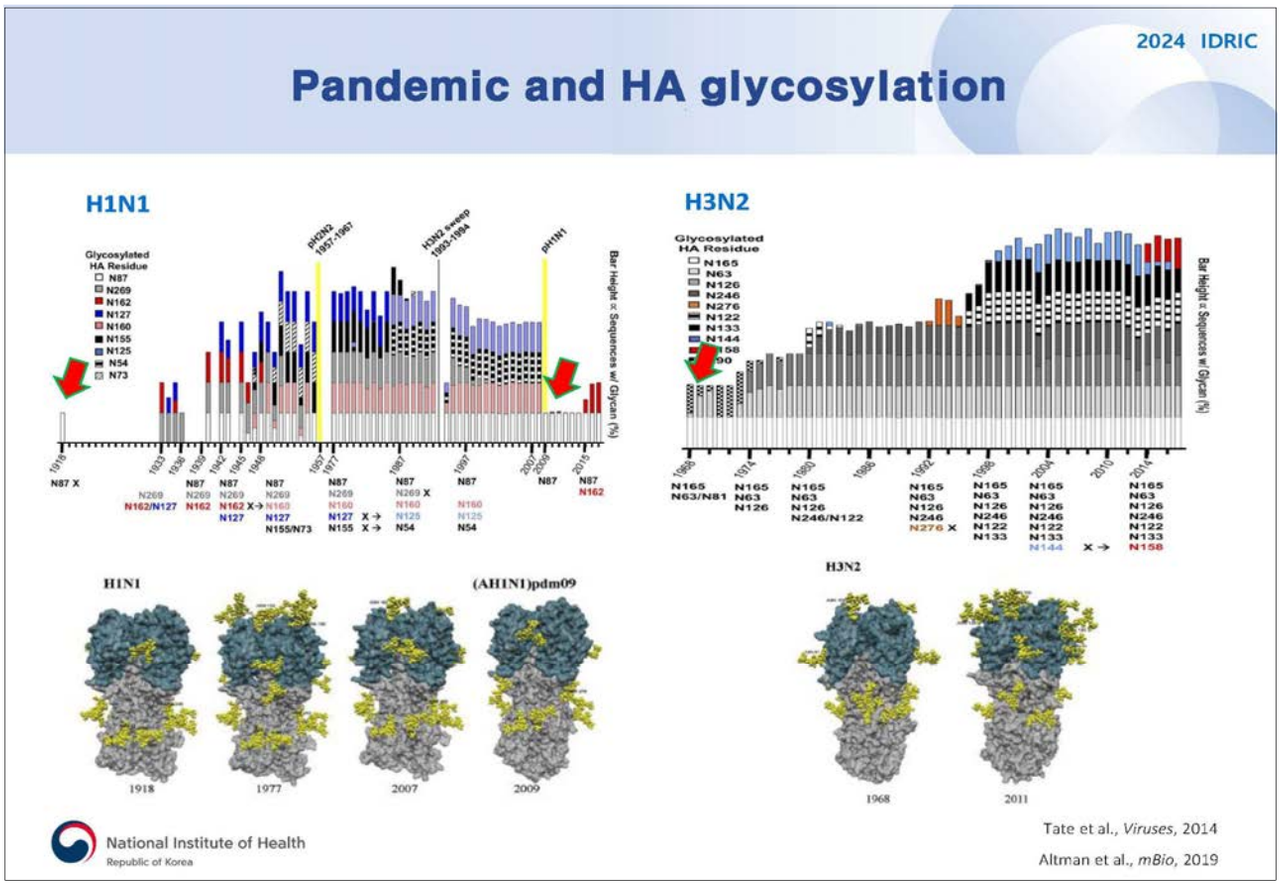
Pathogenesis of recombinant maH3N2 viruses



National Institute of Health
Republic of Korea

Choi et al., *PLOS ONE*, 2020

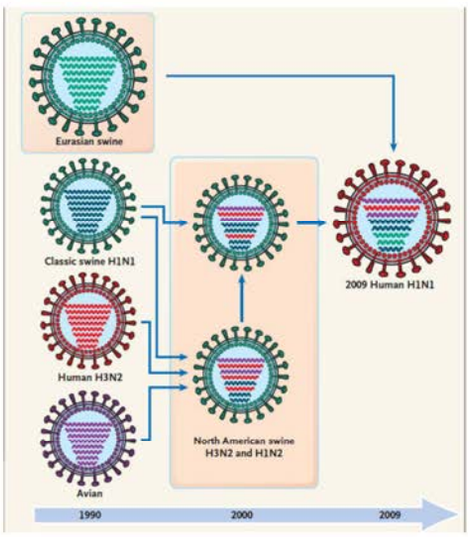

2024 IDRIC
Pathogenesis of recombinant maH3N2 viruses
Control
RG_SW
PB2 mutant
HA mutant
NP mutant
NA mutant
MA_SW
Viral titer (Log10 TCID50/mL)
Day 3
Day 6
Viral titer (Log10 TCID50/mL)
3 dpi
6 dpi
Kidney
Intestine
National Institute of Health
Republic of Korea


2024 IDRIC
Pandemic and HA glycosylation
H1N1
H3N2
Glycosylated HA Residue
Bar Height = Sequences w/ Glycan (%)
pH2N2 1957-1967
H3N2 sweep 1993-1994
pH1N1
(AH1N1)pdm09
1918
1977
2007
2009
1968
2011
National Institute of Health
Republic of Korea
Tate et al., Viruses, 2014
Altman et al., mBio, 2019

2024 IDRIC

Pandemic and HA glycosylation

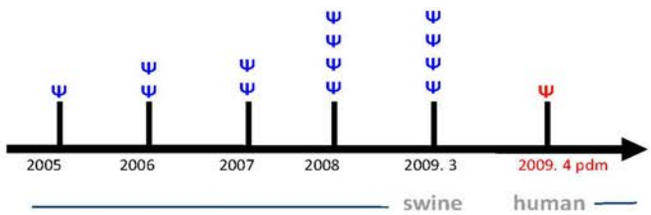
Origin of 2009 pandemic H1N1 virus



Trifonov et al., *NEJM*, 2009

Swine/North American/H1N2/2005-2009.03 HA Glycosylation number

No. GLY	2005	2006	2007	2008	2009 (01-03)
Max	1	2	2	4	4
Min	1	1	1	2	3
Avg	1	1.5	1.6	3.2	3.3



Swine H1 glycosylation

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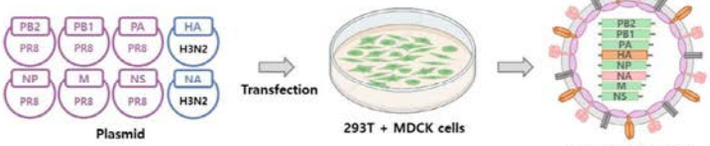
Decreased glycosylation when it cross to new host

2024 IDRIC

Generation of mutant viruses

Recombinant viruses by Reverse Genetics



바이러스	역가 ($TCID_{50}$/ml)	내부 유전자	HA	NA
SW-WT:PR8	2.47×10^8	PR8	SW-HA	SW-NA
SW-N160D:PR8	3.98×10^8		SW-HA N160D	SW-NA
SW-T183A:PR8	2.7×10^8		SW-HA T183A	SW-NA
SW-N262T:PR8	1.37×10^7		SW-HA N262T	SW-NA
SW-N160D T183A:PR8	3.98×10^8		SW-HA N160D T183A	SW-NA
SW-N160D N262T:PR8	1.17×10^7		SW-HA N160D N262T	SW-NA
SW-T183A N262T:PR8	5.62×10^8		SW-HA T183A N262T	SW-NA
SW-Triple[1]:PR8	1.83×10^7		SW-HA Triple[1]	SW-NA

1) N160D/T183A/N262T

Single
Double
Triple

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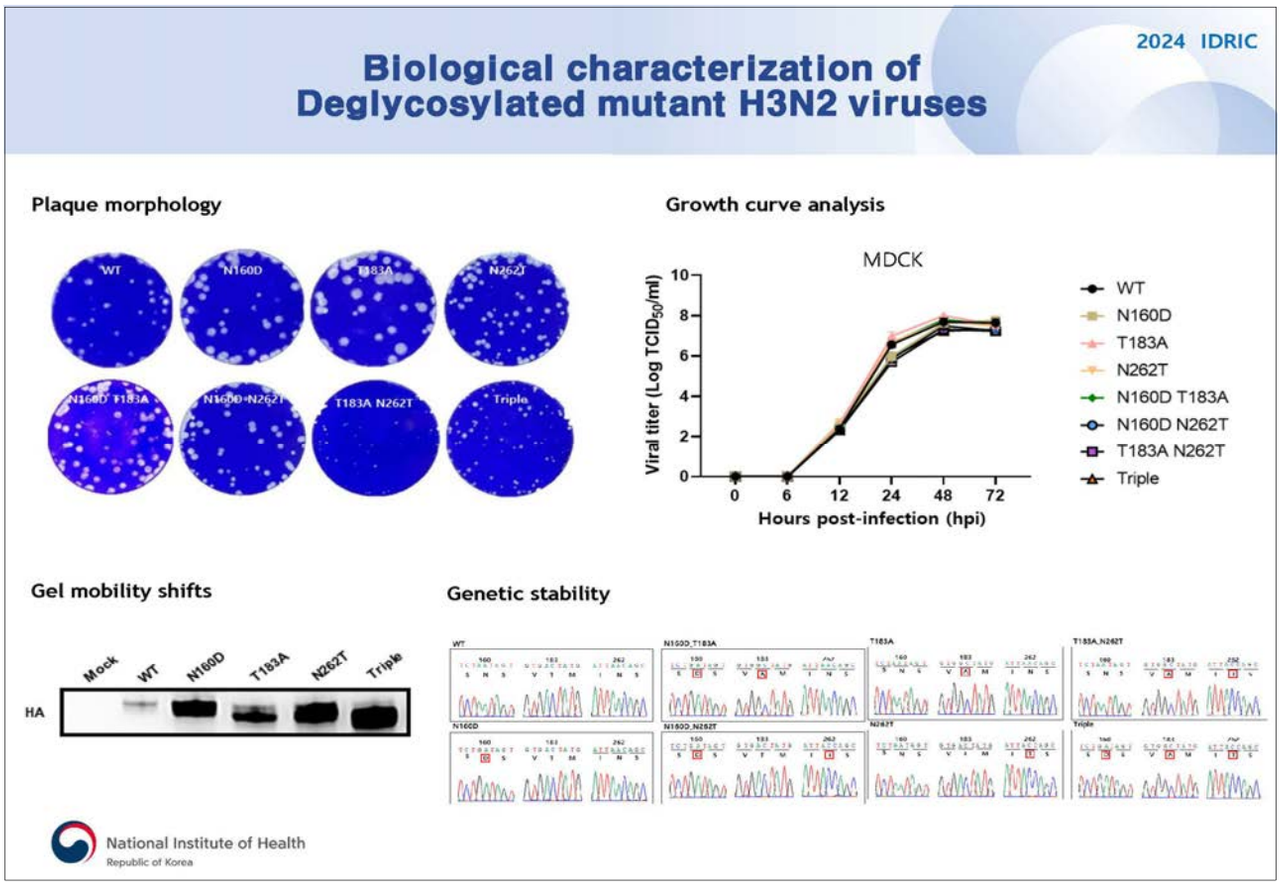
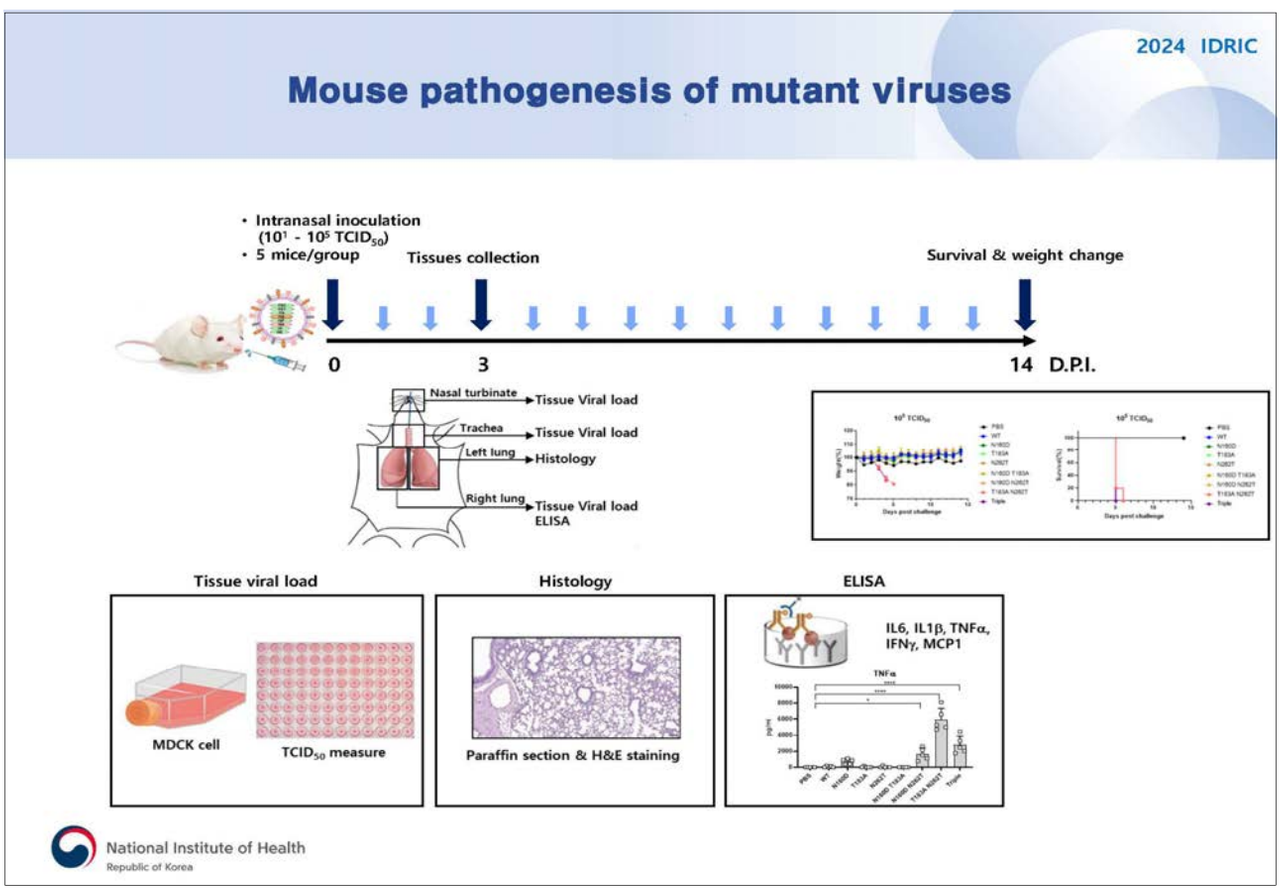
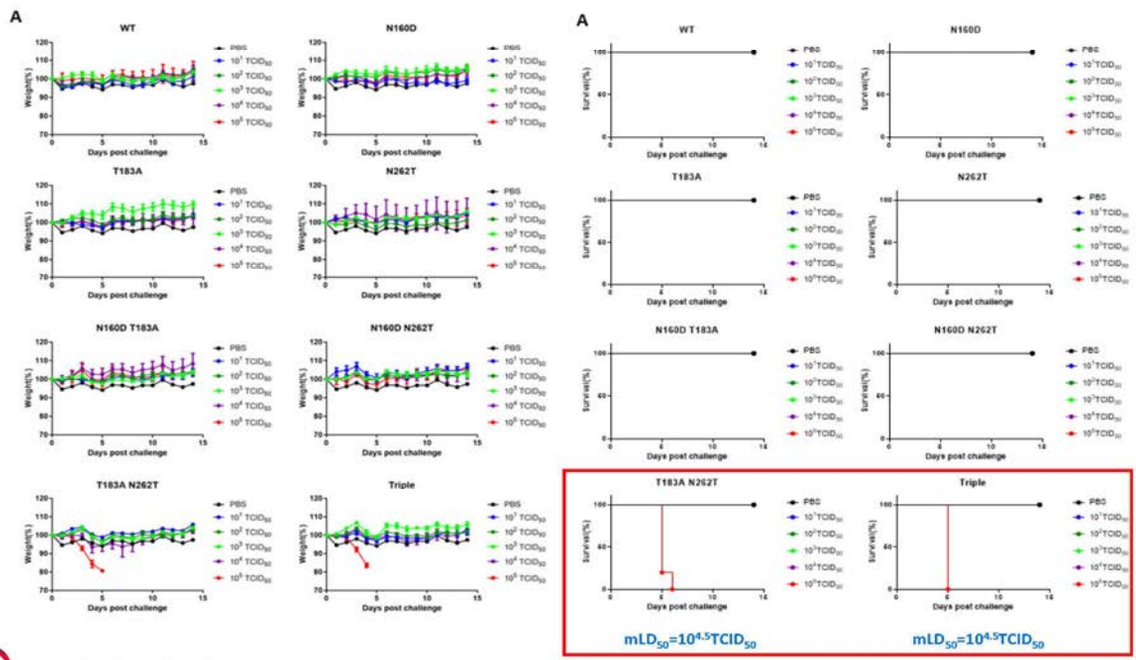
Republic of Korea


2024 IDRIC
Biological characterization of
Deglycosylated mutant H3N2 viruses
Plaque morphology
WT
N160D
T183A
N262T
N160D T183A
N160D N262T
T183A N262T
Triple
Growth curve analysis
MDCK
Viral titer (Log TCID50/ml)
Hours post-infection (hpi)
WT
N160D
T183A
N262T
N160D T183A
N160D N262T
T183A N262T
Triple
Gel mobility shifts
Mock
WT
N160D
T183A
N262T
Triple
HA
Genetic stability
National Institute of Health
Republic of Korea


2024 IDRIC
Mouse pathogenesis of mutant viruses
• Intranasal inoculation
(10¹ - 10⁵ TCID50)
• 5 mice/group
Tissues collection
Survival & weight change
0
3
14 D.P.I.
Nasal turbinate
Tissue Viral load
Trachea
Tissue Viral load
Left lung
Histology
Right lung
Tissue Viral load
ELISA
Tissue viral load
MDCK cell
TCID50 measure
Histology
Paraffin section & H&E staining
ELISA
IL6, IL1β, TNFα,
IFNγ, MCP1
National Institute of Health
Republic of Korea

2024 IDRIC

Pathogenesis of mutant H3N2 viruses in Balb/c mice



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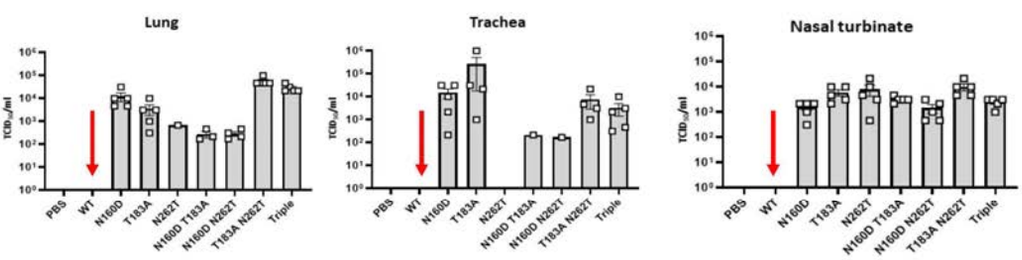
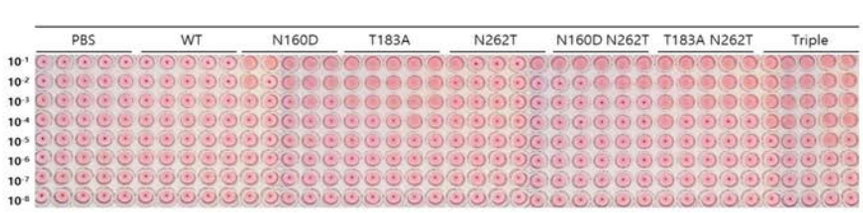
2024 IDRIC

Pathogenesis of mutant H3N2 viruses in Balb/c mice

Virus titers in mice tissues infected with 10^5 TCID$_{50}$ per mouse





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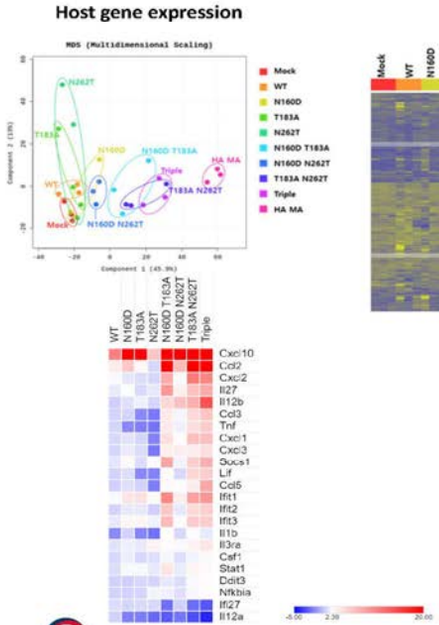
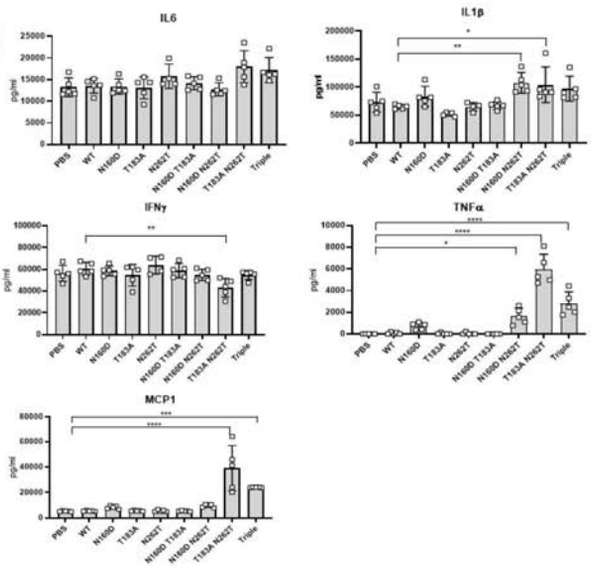
2024 IDRIC

Pathogenesis of mutant H3N2 viruses in Balb/c mice

Host gene expression



Inflammatory cytokine induction in the lung



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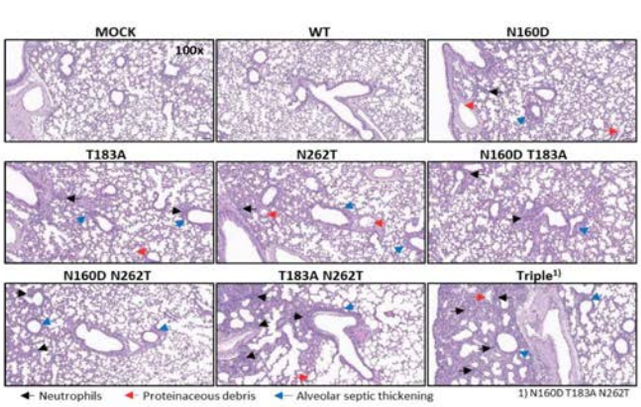
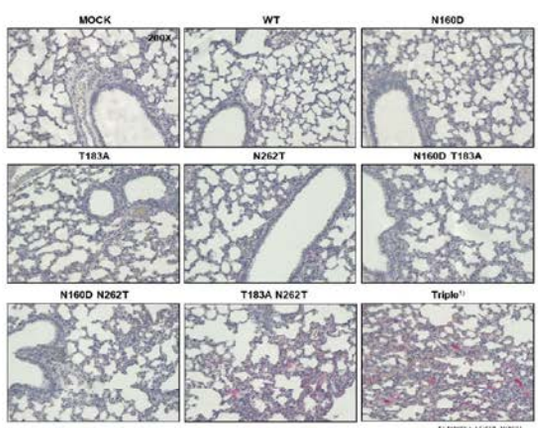
Republic of Korea

2024 IDRIC

Pathogenesis of mutant H3N2 viruses in Balb/c mice

Histopathological lesions and IHC of mouse lung tissue





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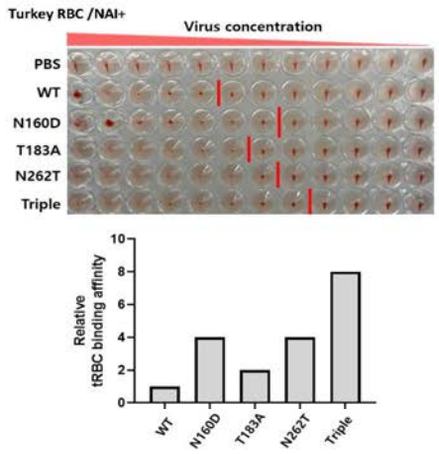
Republic of Korea

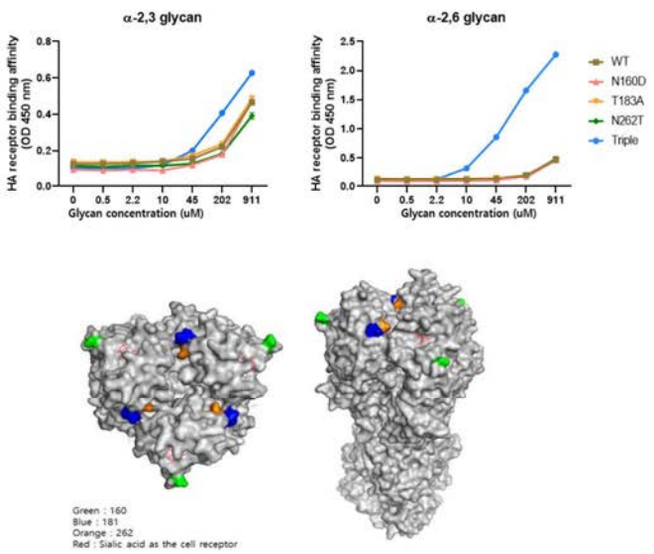
2024 IDRIC

Receptor binding affinity

Hemagglutination assay (HA)



Solid-phase direct virus binding assay



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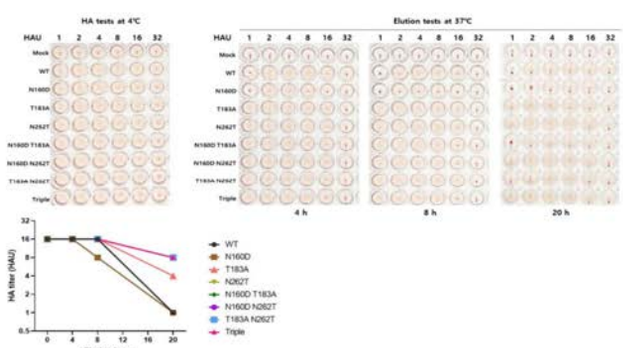
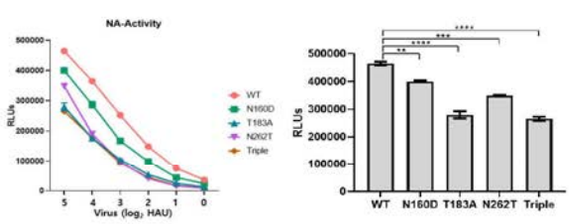
Neuraminidase activity

HA elution assay with tRBCs



Neuraminidase activity assay



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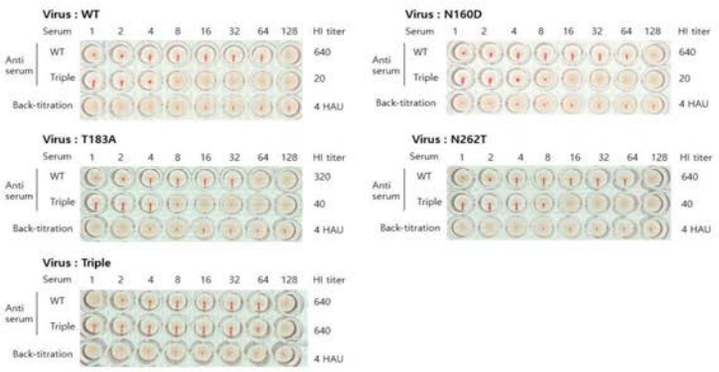
2024 IDRIC

Antigenicity change

Hemagglutination Inhibition (HI) assay



Virus \ Anti serum	SW-WT:PR8	SW-Triple:PR8
SW-WT:PR8	640	20
SW-N160D:PR8	640	20
SW-T183A:PR8	320	40
SW-N262T:PR8	640	40
SW-Triple[1]:PR8	640	640

1) N160D T183A N262T

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2024 IDRIC

Summary

1. Human H3N2 virus HA was deglycosylated during immune naïve mouse adaptation
2. Deglycosylatin of HA confers viral infectivity and pathogenicity in mice.
3. Deglycosylation of HA altered receptor affinity and NA activity for viral fitness.
4. Glycosylation of HA affects H3N2 virus antigenicity .
5. These data could be useful for pandemic virus risk assessment and vaccine design.

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Republic of Korea

03

국내 Mpox 환자의 임상 증상과 바이러스 배출

김민경 교수
국립중앙의료원

Speaker

Kim, Min-Kyung

- National Medical center
- Professor

EDUCATION:

- 2022 PhD candidate in Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
- 2015 M.P.H., Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
- 2009 M.D., Seoul National University College of Medicine, Seoul, Republic of Korea

PROFESSIONAL EXPERIENCE:

- 2020 ~ 현재 Infectious disease physician, National Medical center
- 2019 ~ 2020 Deputy Director, Korea Centers for Disease Control & Prevention (KCDC) Cheongju, Korea
- 2016 ~ 2019 Epidemic Intelligence Officer, Korea Centers for Disease Control & Prevention (KCDC) Cheongju, Korea
- 2015 ~ 2016 Chief Researcher, Seoul Center for Infectious Disease Control, Seoul, Korea
- 2014 ~ 2015 Fellow, Division of Infectious Disease, Department of Internal Medicine, SNUH, Seoul, Korea
- 2010 ~ 2014 Resident, Department of Internal Medicine, SNUH, Seoul, Korea
- 2009 ~ 2010 Intern, Seoul National University Hospital(SNUH), Seoul, Korea

Topic

Clinical presentation and viral shedding in patients with Mpox in South Korea

Abstract

국내 엠폭스 유행 초기(2022년 9월부터 2023년 6월) 국립중앙의료원에 입원한 엠폭스 환자들을 대상으로 임상적 특성 분석과 함께 구인두, 항문생식기 병변 및 피부 병변에서 monkeypox virus의 PCR 양성 기간과 배양 양성 기간을 분석하였다.

2024 International Symposium for Infectious Diseases Research Institutes Cooperation

Clinical Presentation and Viral Shedding in Patients with Mpox in South Korea

Min-Kyung Kim
National Medical Center

국립중앙의료원 national medical center

Outline

- Background - Global mpox outbreak
- Study methods
- Results (1) - Clinical presentation
- Results (2) - Viral shedding
- Discussion
- Conclusion

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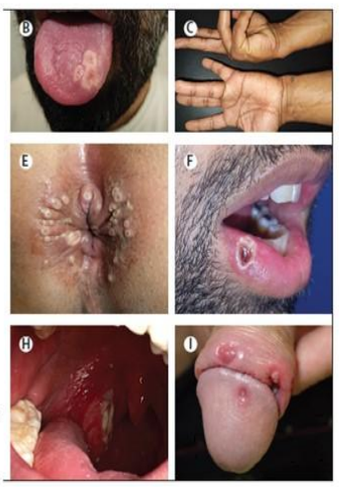
Mpox

- Mpox(formerly Monkeypox), a zoonotic illness caused by the monkeypox virus, an orthopoxvirus and close relative of variola virus (smallpox).
- The clinical syndrome is characterized by fever, rash, and lymphadenopathy.
  - Complications can include pneumonitis, encephalitis, and secondary bacterial infections.
- Mpox has affected rural communities in west and central Africa since the first human case was reported in the DR Congo in 1970.



Clinical presentation of monkeypox
source: Lancet 2022; 400: 661–69

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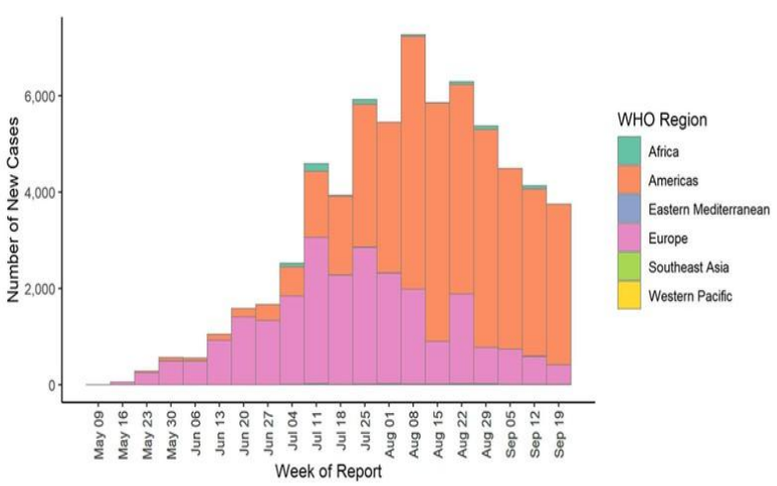
Ann Med Surg (Lond). 2022 Jul; 79: 104069.

Mpox Outbreak-global situation

- However, since detection of monkeypox virus transmission outside endemic areas (UK) in May 2022, a large multi-country mpox outbreak has occurred.



국립중앙의료원 national medical center | **Weekly new monkeypox cases by WHO region globally as of September 23, 2022.**

https://www.cdc.gov/poxvirus/mpox/cases-data/technical-report/report-3.html

Mpox Outbreak-global situation

World Health Organization director general Tedros Adhanom Ghebreyesus, shown in Geneva last year, declared monkeypox a global emergency on Saturday, despite a lack of consensus among members of WHO's emergency committee. (Salvatore Di Nolfi/Keystone/The Associated Press)

WHO Director-General declares the ongoing monkeypox outbreak a Public Health Emergency of International Concern

23 July 2022 | News release | Reading time: Less than a minute (51 words)

On July 23, the WHO Director-General declared the escalating global monkeypox outbreak a Public Health Emergency of International Concern (PHEIC). Currently, the vast majority of reported cases are in the WHO European Region. WHO/Europe remains committed to partnering with countries and communities to address the outbreak with the required urgency.

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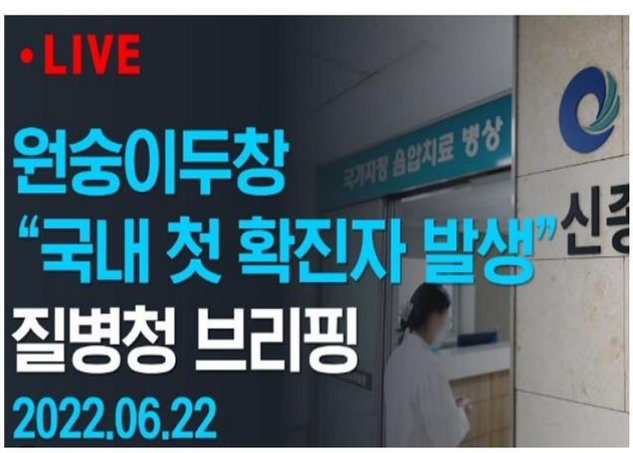
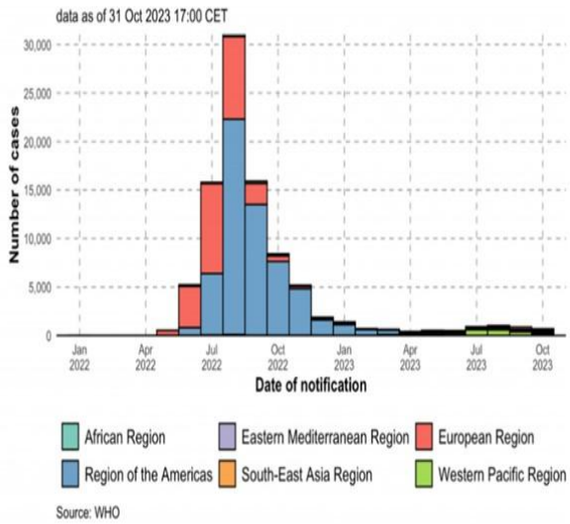
Mpox Outbreak- in South Korea

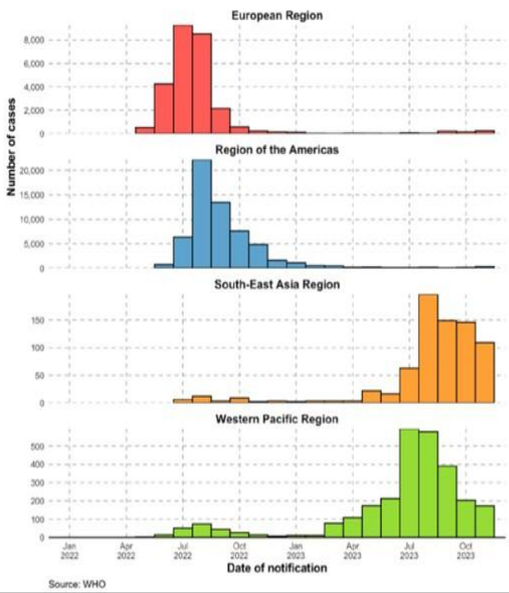


- In Korea, the first mpox case was confirmed in June, 2022. The patient had a travel history to Europe (Germany).
- Subsequently, two more imported cases and one needle stick injury case were confirmed in 2022.

Mpox Outbreak

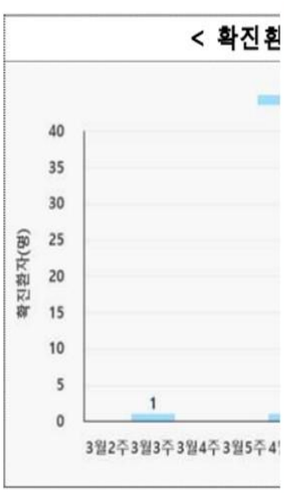
- Although the number of mpox cases worldwide decreased from September 2022, **Western Pacific region experienced late outbreak in 2023**.

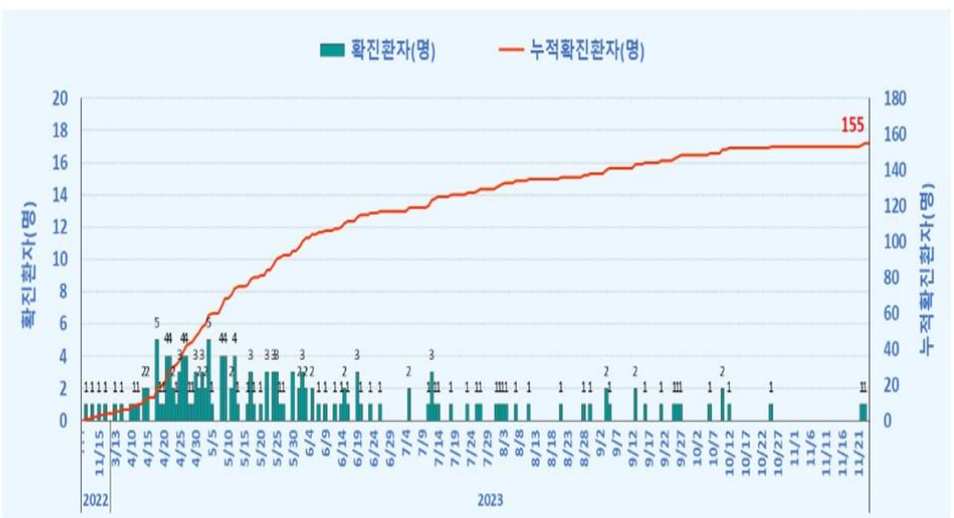




Mpox Outbreak in South Korea

- In South Korea, **domestic outbreak occurred** after the first locally acquired case (the 6th case) was confirmed **in April 2023**.





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national medical center

Purpose of study

- Still, understanding of in-vivo viral kinetics and infectivity is poor and the clinical significance of prolonged viraemia and skin shedding remains uncertain.

- This study **aimed** to describe the **clinical characteristics and viral dynamics of mpox cases** who have been isolated in a referral hospital.

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Methods

- Study design: a prospective observational cohort study
- Participants: **hospitalized patients** with confirmed mpox in the National Medical Center in South Korea between September 1, 2022, and June 15, 2023
  - Patients who consented to participate were included
- Epidemiological and clinical characteristics were reviewed.
- Swabs were collected from the **oropharynx (OP), anogenital lesions (AL) and skin lesions (SL)** on hospital days 1, 2, 4, 7, 10, 13, and 21.
- **Blood samples** were collected on hospital days 1, 7, and 14, and during follow-up visits after discharge
  - Sampling schedules were modified according to each patient's condition and date of discharge.

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Results

Demographic and clinical characteristics of participants (n=18)

Baseline characteristics	n (%) (N=18)
Men, n(%)	17 (94.4)
Age (years), median (IQR)	32.5 (30-34.8)
Imported cases from overseas travel, n(%)	2 (11.1)
Sexual contact before symptom-onset, n(%)	
Homosexual contact	13 (72.2)
Heterosexual contact	4 (22.2)
Denied to report	1 (5.6)
Smallpox or mpox vaccination before diagnosis, n(%)	0 (0)
People living with HIV, n(%)	9 (50)
CD4 count, cells/μL, median (IQR)	547 (494, 692)
History of previous syphilis infection, n(%)	8 (44.4)
Time from symptom onset to mpox diagnostic test (days), median (IQR)	6 (5–7.75)
Length of hospital stay (days)	10 (6.25–11)

Baseline characteristics	n (%) (N=18)
Clinical presentation of mpox, n(%)	n (%) (N=18)
Fever	14 (77.8)
Myalgia	11 (61.1)
Inguinal lymphadenopathy	7 (38.9)
Headache	4 (22.2)
Genital lesion (penile, public, and female vulva)	14 (77.8)
Anal or perianal lesion	14 (77.8)
Other skin lesion (except ano-genital lesion)	10 (55.6)
Con-comittant infection	
Sexually-transmitted disease	7 (38.9)
Peri-lesional cellulitis	4 (27.8)
Treatment	
Tecovirimat	13 (72.2)
Antibiotics for syphilis or con-comittant STD	5 (27.8)
Famciclovir[a]	2 (11.1)
Pain killer	15 (83.3)
Antihistamine	10 (55.6)

J Korean Med Sci. 2024 Jan 29;39(4):e19
https://doi.org/10.3346/jkms.2024.39.e19

JKMS

Table 1. Demographic and baseline characteristics of the patients

Variables	All patients (N = 60)
Age, yr, median (range)	32 (21-58)
Male	58 (97)
Nationality	
Republic of Korea	54 (90)
China	1 (2)
Japan	1 (2)
Philippine	1 (2)
Taiwan	1 (2)
Russia	1 (2)
Vietnam	1 (2)
Race	
Asian	59 (98)
White	1 (2)
Sexual orientation	
Homosexual/bisexual	51 (85)
Unknown	9 (15)
HIV infection	
Negative	35 (58)
Previously diagnosed	18 (30)
Newly diagnosed	7 (12)
Concomitant STI, No. of cases/No. of tested (%)	15 (25)
Neisseria gonorrhoeae	2/51 (4)
Mycoplasma genitalium	1/51 (2)
Mycoplasma hominis	1/51 (2)
Ureaplasma species	10/51 (20)
Ureaplasma urealyticum	5/51 (10)
Ureaplasma parvum	4/51 (8)
Unknown species	1/51 (2)
Gardnerella vaginalis	4/51 (8)
Primary or secondary syphilis	4/59 (7)
Jynneos vaccination	4 (7)
PrEP	1 (2)
PEP	2 (3)
Vaccination after recovery from Mpox	1 (2)

Table 2. Clinical manifestation, diagnosis, and treatment of the patients

Variables	All patients (N = 60)
Initial presenting symptoms	
Constitutional symptoms	53 (88)
Pain or mucocutaneous lesions in anogenital area	28 (47)
Extragenital mucocutaneous lesions	29 (48)
Clinical symptoms	
Fever (> 38°C)	13 (22)
Sweat	8 (13)
Sore throat	16 (27)
Chills	27 (45)
Cough	1 (9)
Lymphadenopathy (all inguinal)	9 (15)
Headache	11 (18)
Myalgia	23 (38)
Back pain	1 (2)
General weakness	6 (10)
Fatigue	7 (12)
Pruritis	1 (2)
Conjunctivitis	1 (2)
Nausea/vomiting	1 (2)
Anal pain or discharge	7 (12)
Proctitis	3 (5)
Skin lesions	60 (100)
Initial skin manifestation	
Maculopapular	36 (60)
Vesiculopustular	49 (82)
Eschar	13 (22)
Site of skin lesions	
Face	28 (47)
Trunk or limbs	48 (80)
Palms or soles	21 (35)
Anogenital area	51 (85)

J Korean Med Sci. 2024 Jan 29;39(4):e19

PCR/culture positive rate by specimen

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Detection of MPXV DNA and infectious virus shedding

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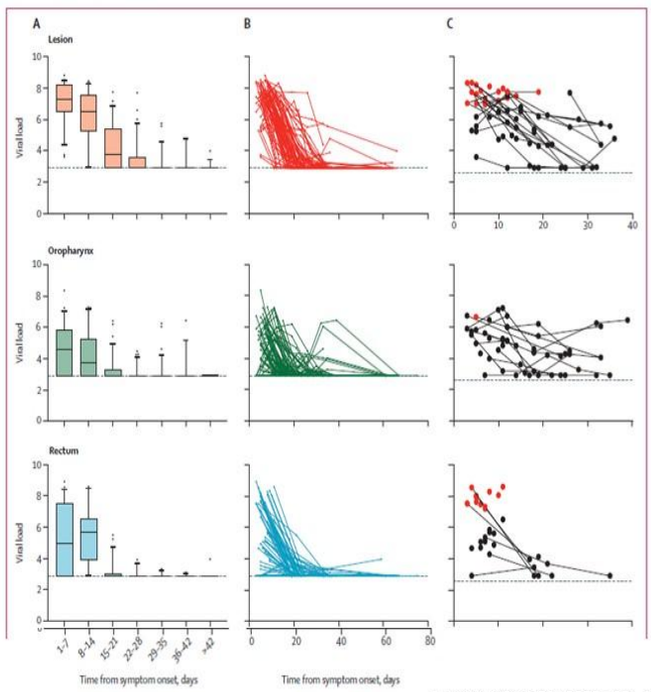
Viral shedding by specimen

Discussion

Viral dynamics in patients with monkeypox infection: a prospective cohort study in Spain

- An prospective, multicentre study of mpox outpatients in Spain, June 28 - Sept 22, 2022.
- **Participants were asked to collect** samples from their **skin lesions, oropharynx, and blood** (dried blood spot) on days **1, 8, 15, 22, 29, and 57** after the screening visit, and samples from their **rectum (swab), semen (collection container), and vagina (swab) on days 1, 15, 29, and 57.**



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Lancet Infect Dis 2023; 23: 445–53

Systematic Reviews

Viral load dynamics and shedding kinetics of mpox infection: a systematic review and meta-analysis

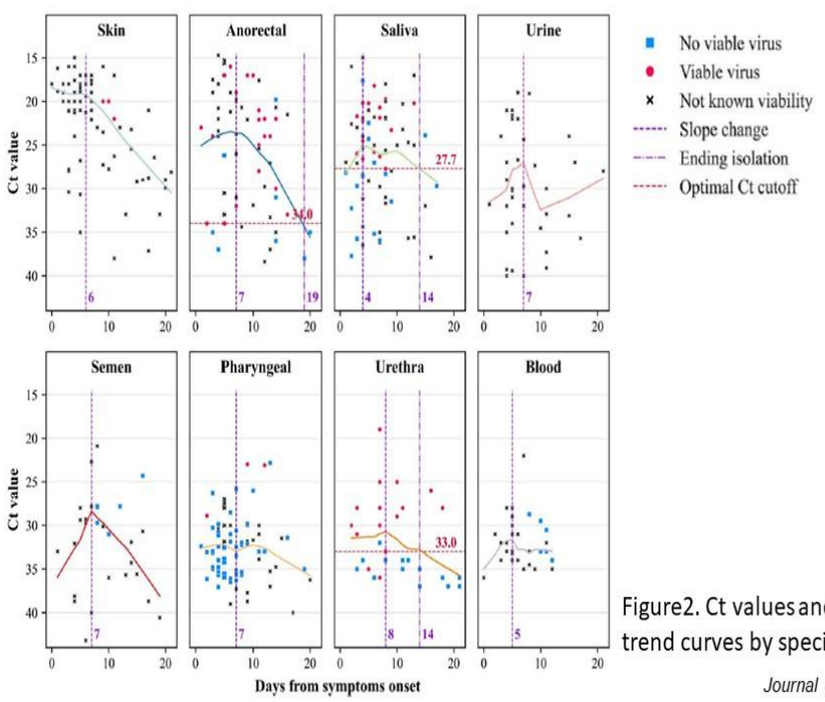

Figure2. Ct values and its temporal trend curves by specimen types

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Journal of Travel Medicine, 2023, 1–10

Limitations

- First, most participants did not have samples collected after discharge, we could **not** determine the **maximum duration** of viral shedding.
- Second, the interval of sample collection and duration of follow up differed among participants.
- Third, the number of participants and number of samples was relatively small. However, we cultured all samples with positive PCR results, to maximize the amount of data on viable virus from the available samples.

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Conclusion

- Viral DNA was detected for up to 23, 19, and 15 days from symptom onset in AL, SL, and OP samples, respectively and infectious virus was isolated for up to 15 days from symptom onset in all three sample types.

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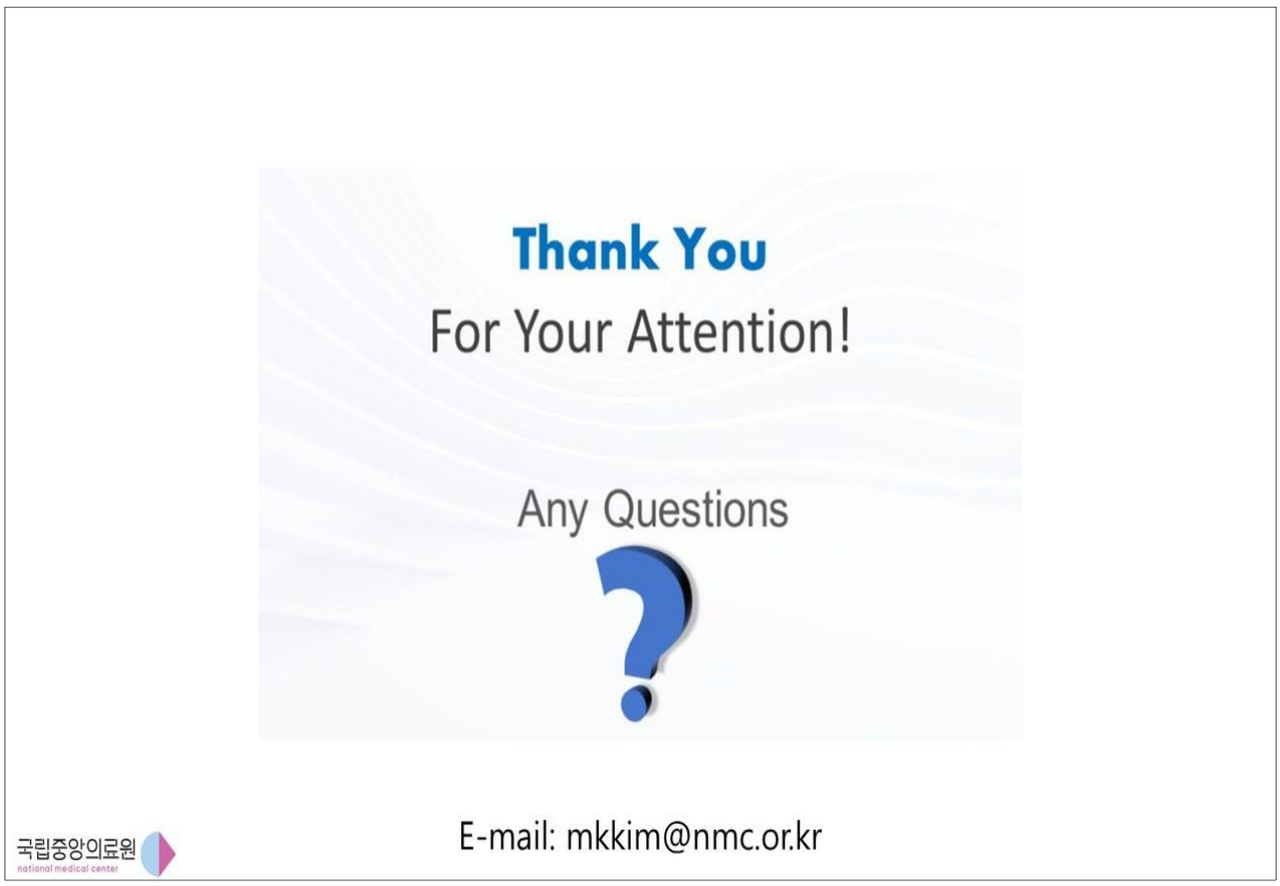
Thank You
For Your Attention!
Any Questions
E-mail: mkkim@nmc.or.kr
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04

한국의 코로나19 후유증 조사연구 사업

이재갑 교수
한림대학교

Speaker

Jacob Lee

- Hallym University college of Medicine
- Associate Professor

EDUCATION:

- 2016 Korea University Graduate School, Ph.D.
- 2003 Korea University Graduate School, Master of Medicine
- 1999 Korea University, MD

PROFESSIONAL EXPERIENCE:

- Present Associate Professor, Hallym University college of Medicine
- 2022 ~ Present Long COVID-19 Syndrome Research Leader
- 2020 ~ Present Korea Disease Control and Prevention Agency Infectious Disease Crisis Management Committee Member
- 2018 ~ Present Small and Medium Hospital Infection Control Consulting System Manager
- 2021 ~ 2022 Daily Life Restoration Support Committee Medical Quarantine Division Member
- 2020 ~ 2021 Central Disaster and Safety Countermeasures Committee Member
- 2015 Ebola Emergency Relief Team (2nd Leader)
- 2004 ~ 2007 International Cooperation Volunteer (Kazakhstan) KOICA

Topic

Long-COVID Research Project in Korea

Abstract

Overview:

- The NIID initiated a research project on the long-term sequelae of COVID-19 (long-COVID) in 2021.
- A consortium of Hallym University, Gachon University, and Seoul Asan Hospital is conducting the research.
- The project period is from 2021 to the end of 2025.

Research Objectives:

- To investigate the epidemiology and characteristics of long-COVID.
- To analyze the risk factors and prognosis of long-COVID.
- To develop treatment and management strategies for long-COVID.

Research Methods:

- A cohort of 10,000 individuals will be assembled to investigate the epidemiology and characteristics of the disease.
- Clinical records of the cohort will be computerized and linked to Korean National Health Insurance data to analyze the characteristics of long-COVID patients.
- Big data information from the Korea Disease Control and Prevention Agency (KDCA) and health insurance information will be linked to analyze the nationwide epidemiology of long-COVID.
- Clinical specimens from the established cohort will be utilized to study the mechanisms of long-COVID, including cognitive impairment, chronic fatigue syndrome, and respiratory complications.


. Long COVID, post COVID condition – research in Korea
한국의 코로나19 후유증 조사연구 사업
Hallym University College of Medicine
Dept of IM, Div. of Infectious Diseases
Jacob Lee


PASC
Long COVID

Long-COVID

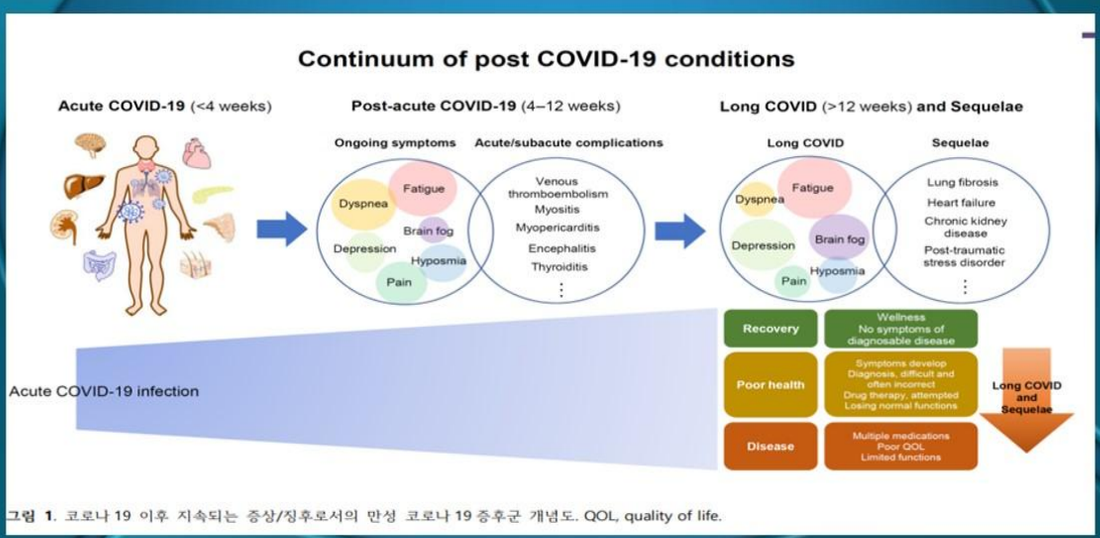


그림 1. 코로나 19 이후 지속되는 증상/징후로서의 만성 코로나 19 증후군 개념도. QOL, quality of life.

만성 코로나 19 증후군(Long COVID) 진료지침 예비 권고안, 2022년

WHO definition : Post-COVID19 Condition

- Post-COVID Conditions, also known as long COVID, are defined as symptoms that persist for at least 2 months after the onset of COVID-19 symptoms, and cannot be explained by other alternative diagnoses.

Definition

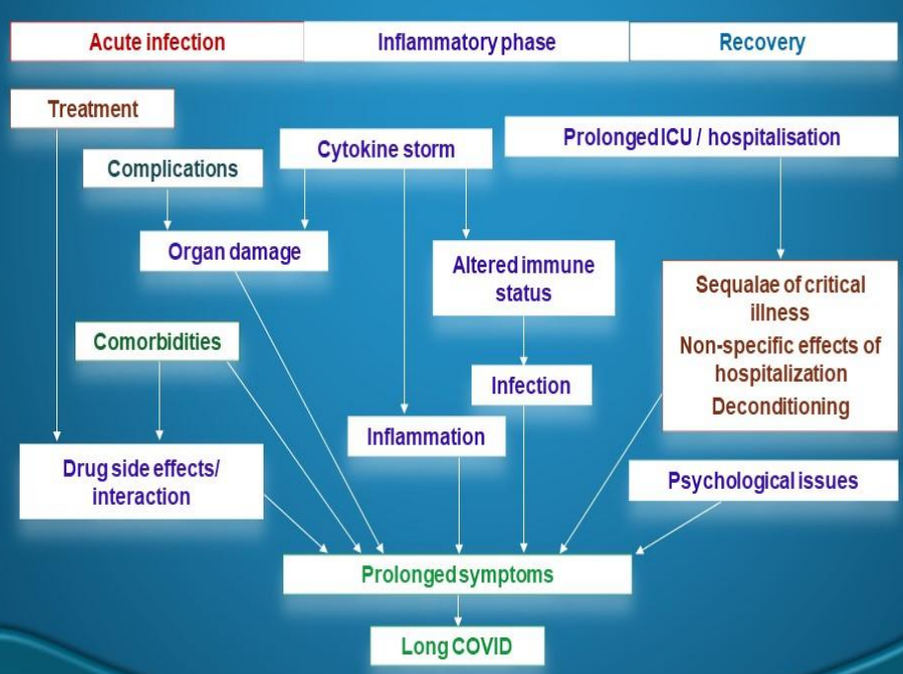
- Different definitions of long COVID from different organizations:

- UK NICE
  - Ongoing symptomatic COVID-19: Symptoms or signs that persist for at least 4-12 weeks after diagnosis and improve within 12 weeks.
  - Post-COVID-19 syndrome: Symptoms or signs that persist for more than 12 weeks.

- US NIH
  - Post-acute sequelae of SARS-CoV-2 infection: Symptoms or signs that persist for more than 2 weeks after acute COVID-19.

- Korean Society of Infectious Diseases (Preliminary Recommendations for the Treatment Guidelines for Long COVID, 2022)
  - Post-acute COVID-19: Symptoms or signs that persist for at least 4 weeks after diagnosis and cannot be explained by other diseases.
  - Long COVID: Symptoms or signs that persist for more than 12 weeks.

Pathogenesis of long COVID



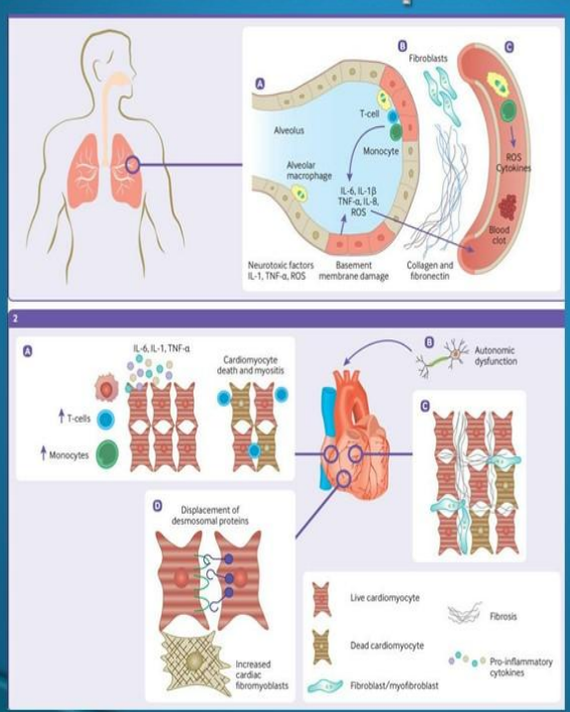
Long COVID is known to have about 200 different symptoms

Chronic COVID-19 syndrome is known to have about 200 different symptoms and presents with a wide range of symptoms. The most common symptoms that can persist for up to six months include fatigue, post-exertional malaise, and cognitive dysfunction.

- Pain in various parts of the body
- Shortness of breath
- Cough
- Joint/muscle pain
- Chronic fatigue
- Fever
- Diarrhea
- Abdominal pain
- Sleep disturbances
- Depression
- Hair loss, rash

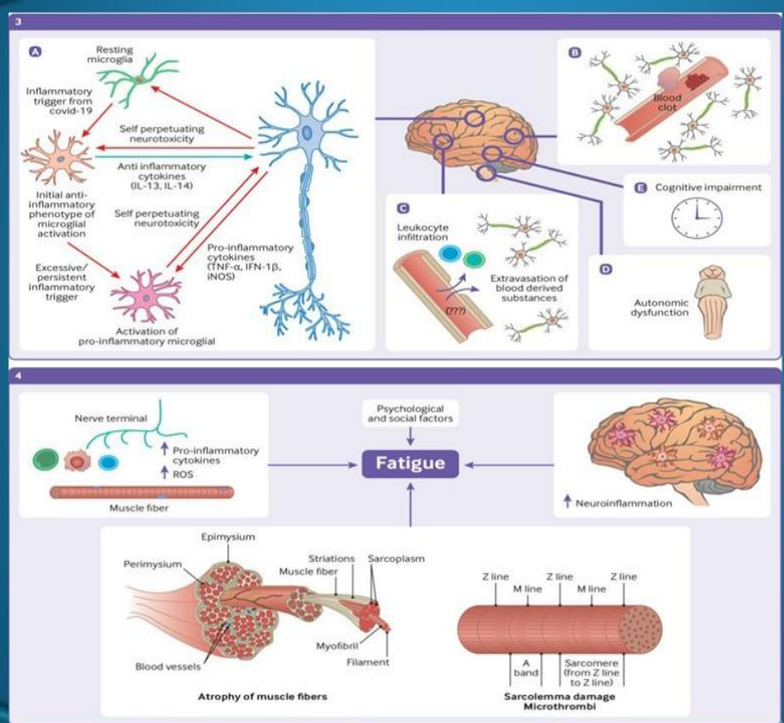
Davis H, et al. Nat Rev Microbiol.2023;21(3):133-146. 2. Davis H, et al. EClinicalMedicine.2021;38:101019

Long COVID-19 : cardiopulmonary involvement



BMJ 2021;374:n1648

Long COVID-19 : neurologic symptom



BMJ 2021;374:n1648

Development of a Definition of Post acute Sequelae of SARS-CoV-2 Infection

Figure 1. RECOVER Adult Analysis Cohort

- **13 754** Adults enrolled as of April 10, 2023
  - **4295** Met World Health Organization criteria for SARS-CoV- 2 within 30 d of infection enrolled in the acute infected cohort
    - **1375** Excluded
      - **1319** Did not reach end of window for at least 1 visit ≥6 mo after index
      - **56** Did not start protocol
    - **2920** Reached end of window for at least 1 visit ≥6 mo after index[b]
      - **2248** Attended at least 1 visit ≥6 mo after index and started symptom survey
        - **17** Pre-Omicron wave
        - **2231** Omicron Wave
  - **7368** Met World Health Organization criteria for SARS-CoV- 2 infection >30 d prior enrolled in the postacute infected cohort
    - **296** Excluded
      - **207** Did not reach end of window for at least 1 visit ≥6 mo after index
      - **89** Did not start protocol
    - **7072** Reached end of window for at least 1 visit ≥6 mo after index[b]
      - **6398** Attended at least 1 visit ≥6 mo after index and started symptom survey
        - **3732** Pre-Omicron wave
        - **2666** Omicron Wave
  - **2091** Enrolled without infection in the uninfected cohort[a]
    - **744** Excluded
      - **492** Did not reach end of window for at least 1 visit ≥6 mo after index
      - **219** On-study infection before reaching end of window for at least 1 visit ≥6 mo after index
      - **33** Did not start protocol
    - **1347** Reached end of window for at least 1 visit ≥6 mo after index without an on-study infection[b]
      - **1118** Attended at least 1 visit ≥6 mo after index and started symptom survey
        - **292** Pre-Omicron wave (290 postacute cohort)
        - **826** Omicron Wave (438 postacute cohort)

JAMA.2023;329(22):19341946.doi:10.1001/jama.2023.8823

Development of a Definition of Post acute Sequelae of SARS-CoV-2 Infection

Table 2. Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

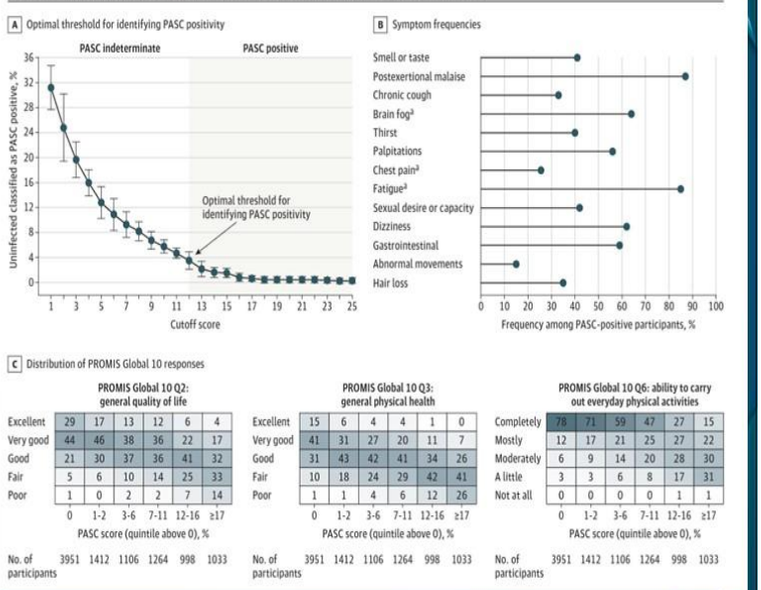
Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

Abbreviation: PASC, postacute sequelae of SARS-CoV-2 infection.

[a] Least absolute shrinkage and selection operator was used to identify which symptoms defined PASC. A symptom score was assigned by dividing the estimated log odds ratio by 0.10 and rounding to the nearest integer. For each person, the total score was defined as the sum of the scores for each symptom a person reported.

[b] Additional severity criteria required (eTables 1 and 2 in Supplement 3).

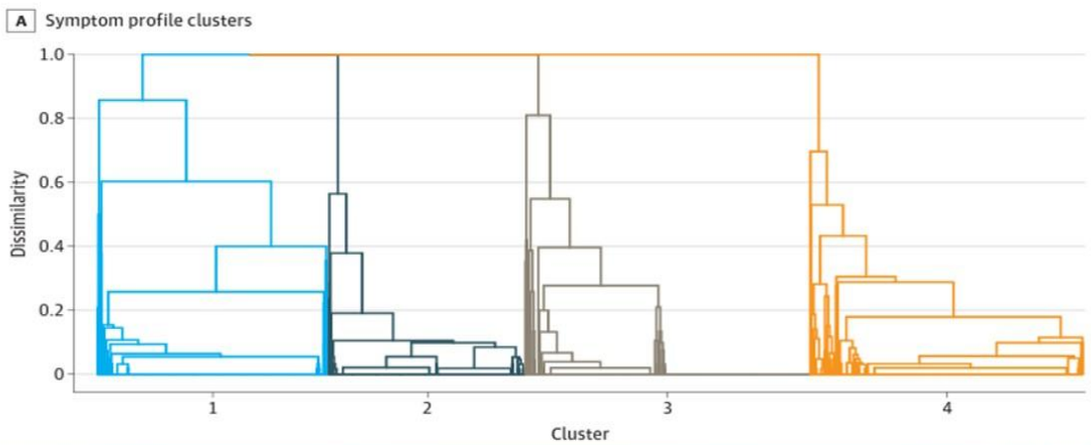
Figure 2. Defining the Postacute Sequelae of SARS-CoV-2 Infection (PASC) Score and a Decision Rule



JAMA.2023;329(22):19341946.doi:10.1001/jama.2023.8823

Development of a Definition of Post acute Sequelae of SARS-CoV-2 Infection

Figure 3. Identification of Postacute Sequelae of SARS-CoV-2 Infection (PASC) Subgroups and Their Characteristics



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코로나19 후유증 조사연구사업(R&D)

빅데이터 기반 코로나19 후유증 연구

가천대학교 길병원 예방의학교실

정재훈

13

Correlation between COVID-19 vaccination and risk of myocardial infarction and ischemic stroke

한림대학교의료원 HALLYM UNIVERSITY MEDICAL CENTER

가천대 길병원 서울아산병원 Asan Medical Center

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Research Letter

ONLINE FIRST FREE

July 22, 2022

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

Young-Eun Kim, PhD[1]; Kyungmin Huh, MD[2]; Young-Joon Park, MD, MPH[3]; Kyong Ran Peck, MD, PhD[3]; Jaehun Jung, MD, PhD[4]

Author Affiliations | Article Information

JAMA. Published online July 22, 2022. doi:10.1001/jama.2022.12992

COVID-19 Resource Center

코로나19 후유증 조사연구사업(R&D)

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정재훈

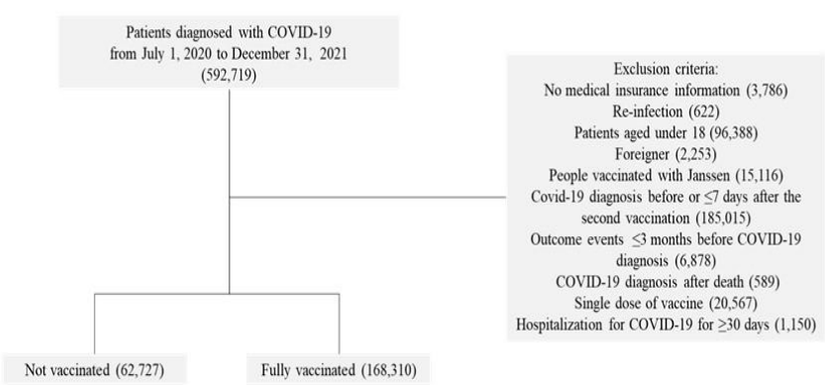
14

Correlation between COVID-19 vaccination and risk of myocardial infarction and ischemic stroke

한림대학교의료원 HALLYM UNIVERSITY MEDICAL CENTER

가천대 길병원 서울아산병원 Asan Medical Center

Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19: Study design



1. Around 590,000 patients aged ≥18 years who were diagnosed with COVID-19, between July 2020 and December 31, 2021 were targeted.
2. A total of 231,037 patients with COVID-19 were included, of whom 62,727 were never vaccinated and 168,310 were fully vaccinated
3. Compared the risk of AMI and ischemic stroke that occurred 31-120 days after COVID-19

코로나19 후유증 조사연구사업(R&D)

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Correlation between COVID-19 vaccination and risk of myocardial infarction and ischemic stroke

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한림대학교의료원 HALLYM UNIVERSITY MEDICAL CENTER

가천대 길병원 | 서울아산병원 Asan Medical Center

Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19: Baseline characteristics

	Unweighted population			Weighted population		
	Not vaccinated 62,727	Fully vaccinated 168,310	Standardized difference	Not vaccinated	Fully vaccinated	Standardized difference
Sex						
Male	30,407 (48.48)	79,176 (47.04)	0.029	45.11	47.21	0.042
Female	32,320 (51.52)	89,134 (52.96)		54.89	52.79	
Age, median [IQR], y	45.4 (18.1)	54.3 (17.1)	0.504	53.4 (20.3)	51.9 (17.6)	0.087
18-39	28,467 (45.38)	36,444 (21.65)		30.39	26.80	
40-64	24,183 (38.55)	80,647 (47.92)		39.71	46.66	
>65	10,077 (16.06)	51,219 (30.43)		29.90	26.51	
Insurance plan for low income	3,308 (5.27)	6,310 (3.75)	0.074	4.47	4.24	0.011
Comorbidities						
Charlson comorbidity index, median [IQR]	0 [0, 2]	1 [0, 2]				
Charlson comorbidity index ≥5	4,001 (6.38)	11,792 (7.01)	0.025	7.26	6.87	0.015
Diabetes	4,479 (7.14)	19,929 (11.84)	0.161	9.17	11.06	0.063
Hypertension	6,782 (10.81)	37,166 (22.08)	0.308	20.07	19.03	0.029
Dyslipidemia	2,254 (3.59)	13,618 (8.09)	0.193	4.25	7.57	0.141
Previous history of outcome events	909 (1.45)	2,704 (1.61)	0.013	2.29	1.46	0.062
Severity of COVID-19						
Severe	6,136 (9.78)	5,298 (3.15)	0.289	12.45	2.84	0.399
Critical	3,514 (5.60)	1,772 (1.05)	0.276	8.52	0.95	0.397

1. Patients who were never vaccinated were younger and less comorbidities. However, there was differences in COVID-19 severity rates
2. After weighting, there was no significant differences in sex, age, insurance plan and comorbidities

코로나19 후유증 조사연구사업(R&D)

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정재훈

Correlation between COVID-19 vaccination and risk of myocardial infarction and ischemic stroke

16

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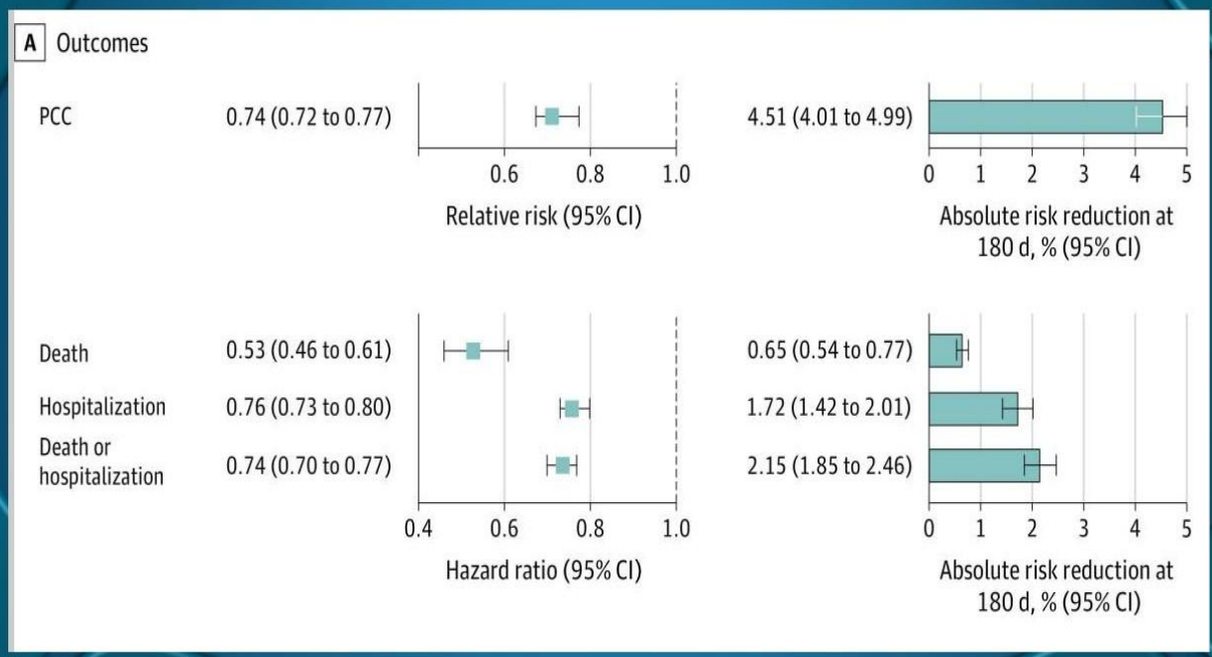
가천대 길병원 | 서울아산병원 Asan Medical Center

Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19: Risk assessment

	Number of events		Incidence per 1,000,000 person-day		Adjusted HR (95% CI)	P Value
	Not vaccinated (62,727)	Fully vaccinated (n=168,310)	Not vaccinated	Fully vaccinated		
Composite outcome	31	74	6.18	5.49	0.42 (0.29–0.62)	<0.001
Acute myocardial infarction	8	24	1.60	1.78	0.48 (0.25–0.94)	0.03
Ischemic stroke	23	50	4.59	3.71	0.40 (0.26–0.63)	<0.001
Subgroup						
Male	17	48	6.98	7.59	0.41 (0.26–0.66)	<0.001
Female	14	26	5.44	3.63	0.42 (0.23–0.76)	0.004
Age, y						
40-64	11	22	5.48	3.39	0.38 (0.20–0.74)	0.004
≥65	20	51	33.99	12.42	0.41 (0.26–0.66)	<0.001
Charlson comorbidity index						
<5	25	56	5.22	4.45	0.40 (0.26–0.60)	<0.001
≥5	6	18	25.04	19.79	0.54 (0.24–1.22)	0.14
Diabetes						
No	23	46	4.89	3.87	0.38 (0.24–0.61)	<0.001
Yes	8	28	26.29	17.58	0.47 (0.25–0.91)	0.03
Hypertension						
No	20	46	4.41	4.39	0.50 (0.31–0.80)	0.004
Yes	11	28	23.11	10.90	0.34 (0.18–0.62)	<0.001
Dyslipidemia						
No	**26**	**67**	**5.24**	**5.05**	**0.44 (0.29–0.65)**	**<0.001**
Yes	5	7	97.55	33.26	0.33 (0.10–1.07)	0.06
Severe or Critical COVID-19						
No	22	65	5.02	5.00	0.37 (0.25–0.55)	<0.001
Yes	9	9	14.38	18.51	0.66 (0.20–2.23)	0.51

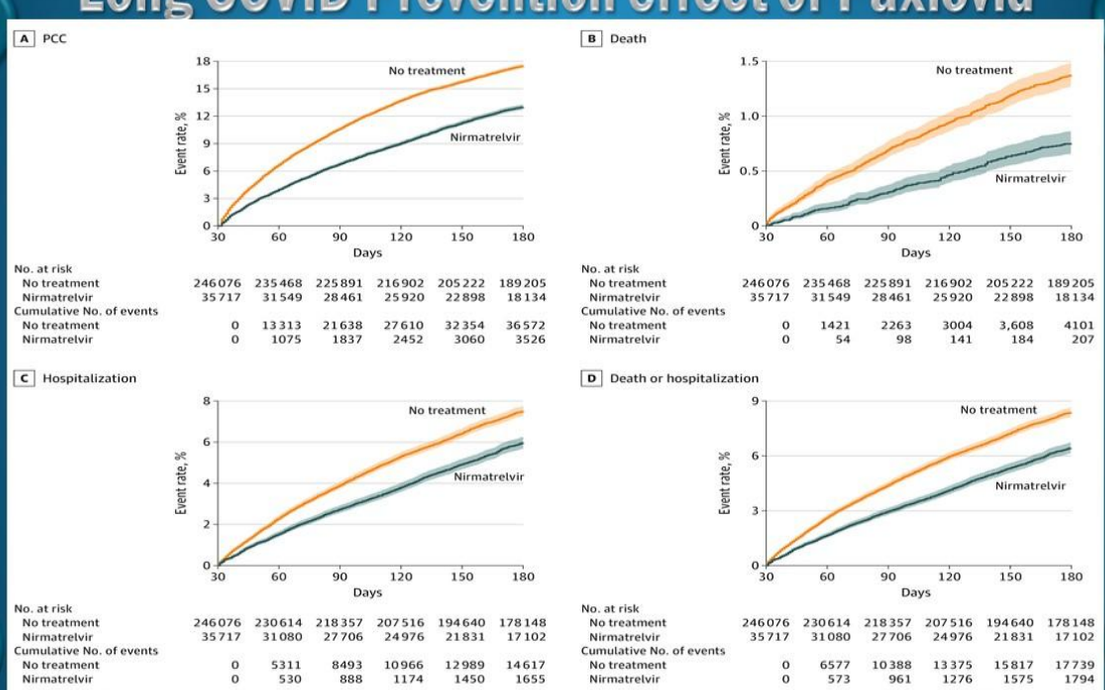
1. A lower risk for outcome events in fully vaccinated patients was observed in most subgroups
2. Reduced risk of AMI and ischemic stroke by 0.37 in vaccinated group, even in mild and severe COVID-19

Long COVID Prevention effect of Paxlovid



JAMA Intern Med. 2023 Mar 23 : e230743.

Long COVID Prevention effect of Paxlovid



No. at risk						
No treatment	246076	235468	225891	216902	205222	189205
Nirmatrelvir	35717	31549	28461	25920	22898	18134
Cumulative No. of events						
No treatment	0	13313	21638	27610	32354	36572
Nirmatrelvir	0	1075	1837	2452	3060	3526

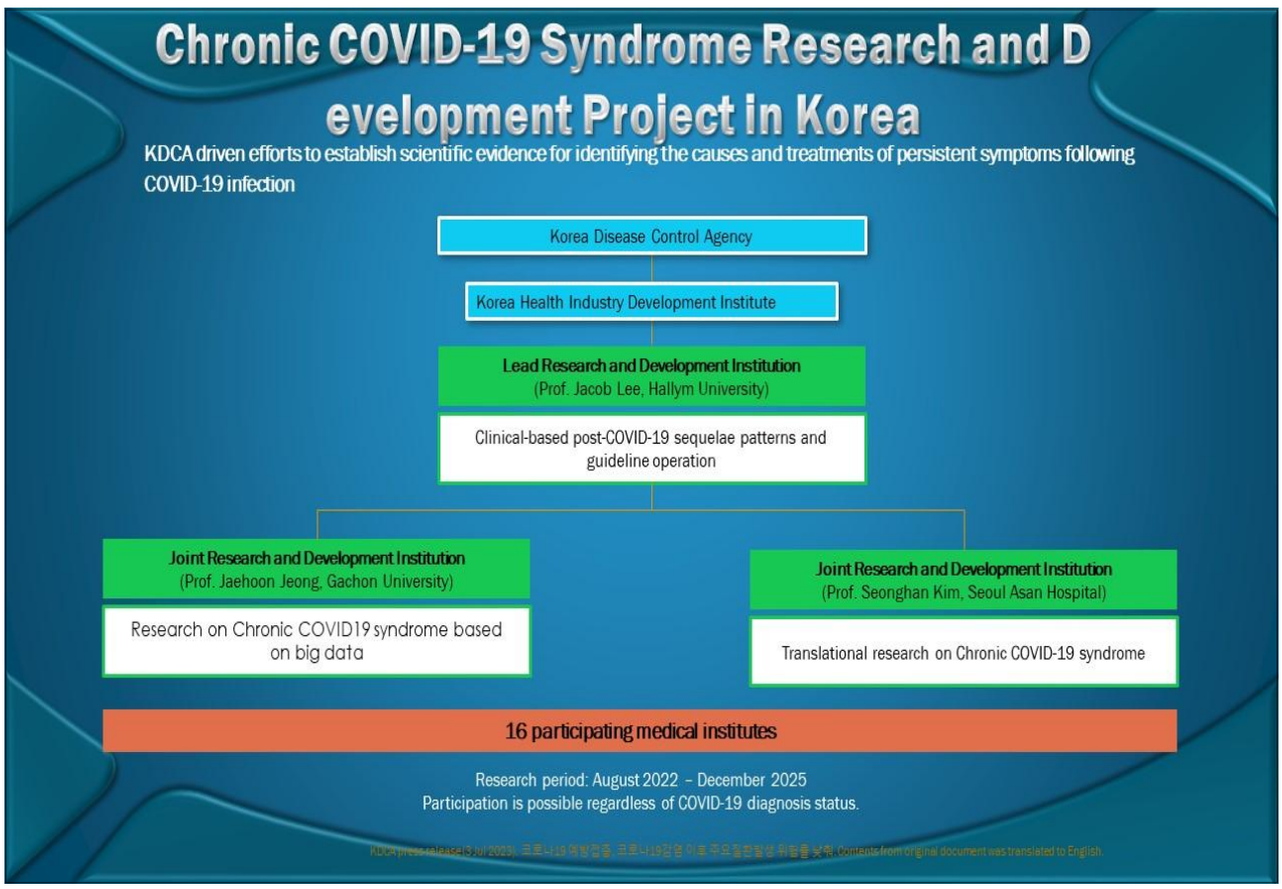
No. at risk						
No treatment	246076	235468	225891	216902	205222	189205
Nirmatrelvir	35717	31549	28461	25920	22898	18134
Cumulative No. of events						
No treatment	0	1421	2263	3004	3,608	4101
Nirmatrelvir	0	54	98	141	184	207

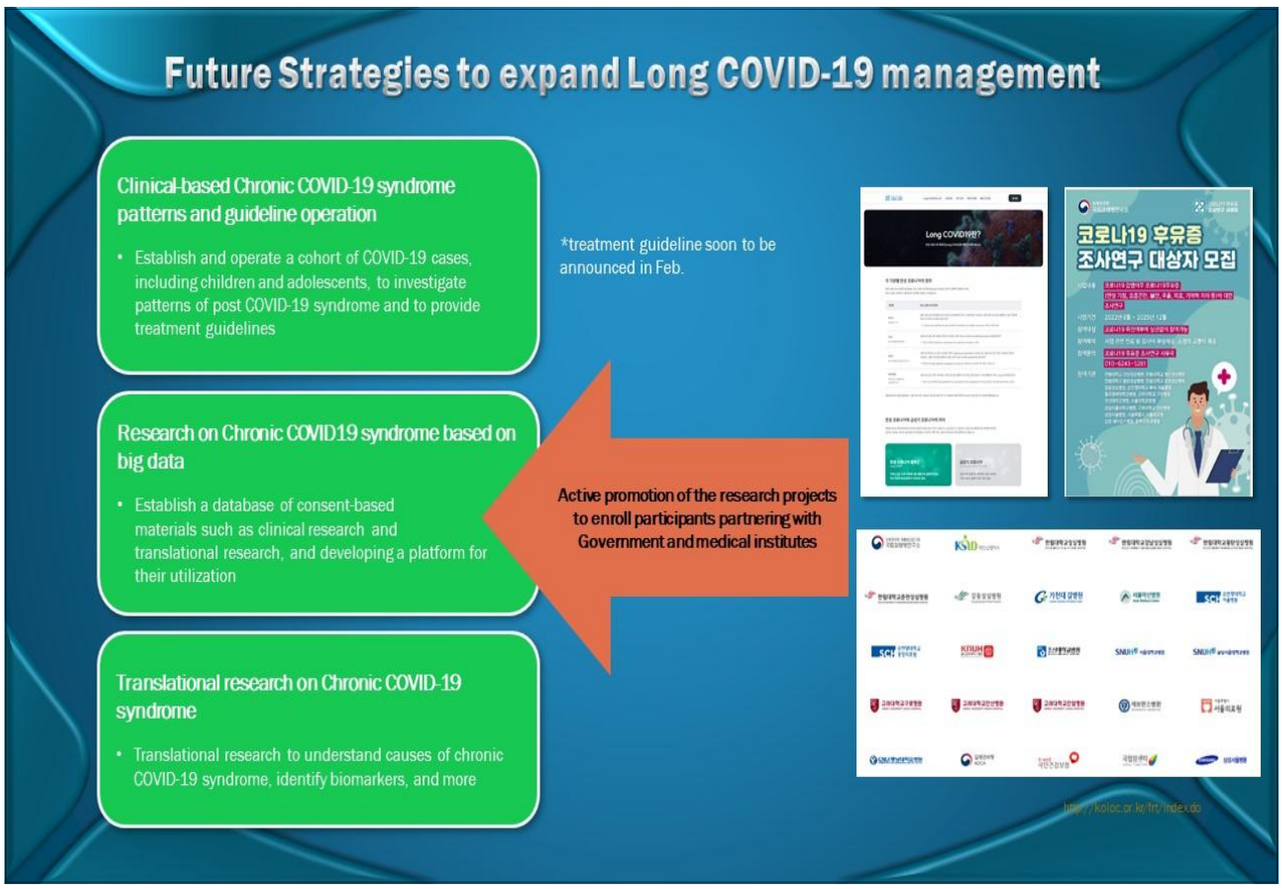
No. at risk						
No treatment	246076	230614	218357	207516	194640	178148
Nirmatrelvir	35717	31080	27706	24976	21831	17102
Cumulative No. of events						
No treatment	0	5311	8493	10966	12989	14617
Nirmatrelvir	0	530	888	1174	1450	1655

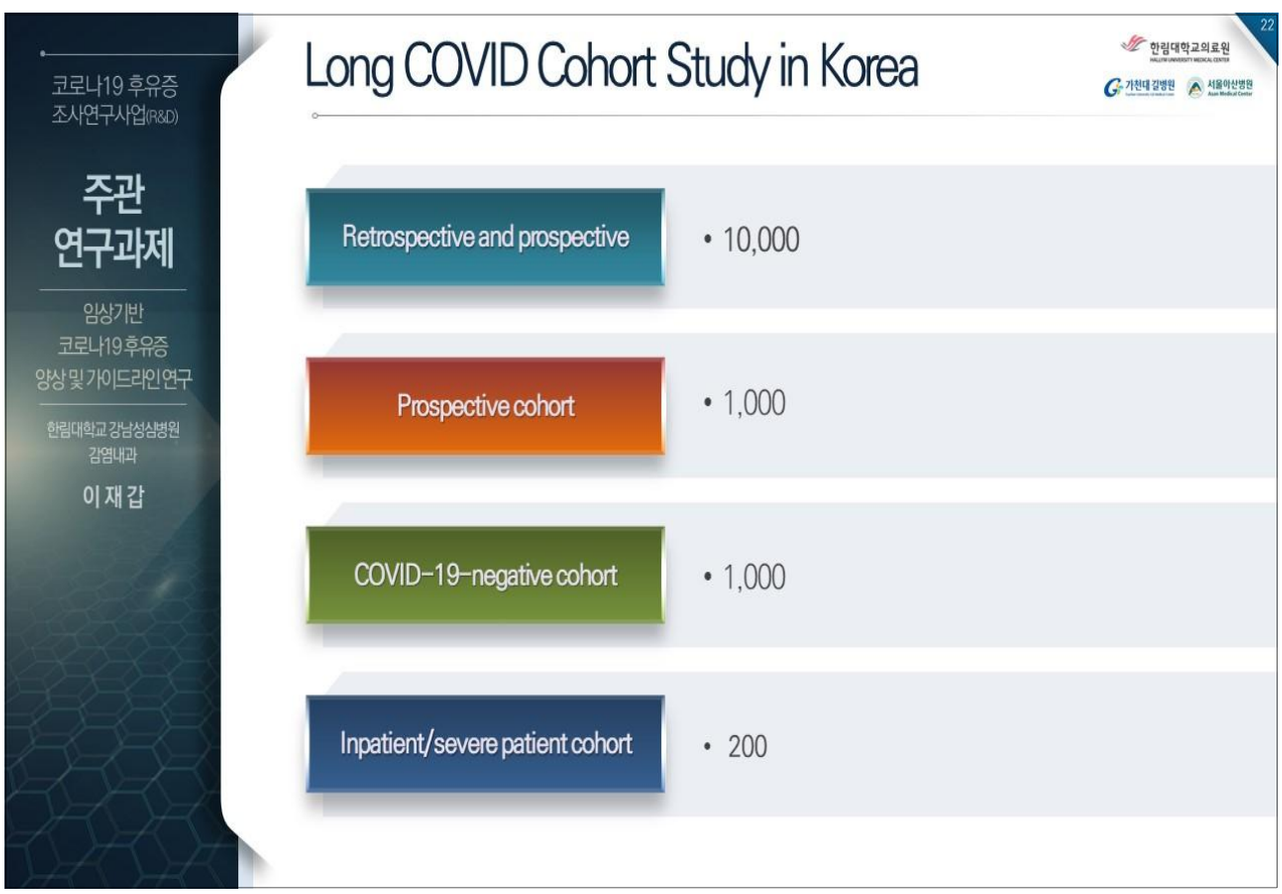
No. at risk						
No treatment	246076	230614	218357	207516	194640	178148
Nirmatrelvir	35717	31080	27706	24976	21831	17102
Cumulative No. of events						
No treatment	0	6577	10388	13375	15817	17739
Nirmatrelvir	0	573	961	1276	1575	1794

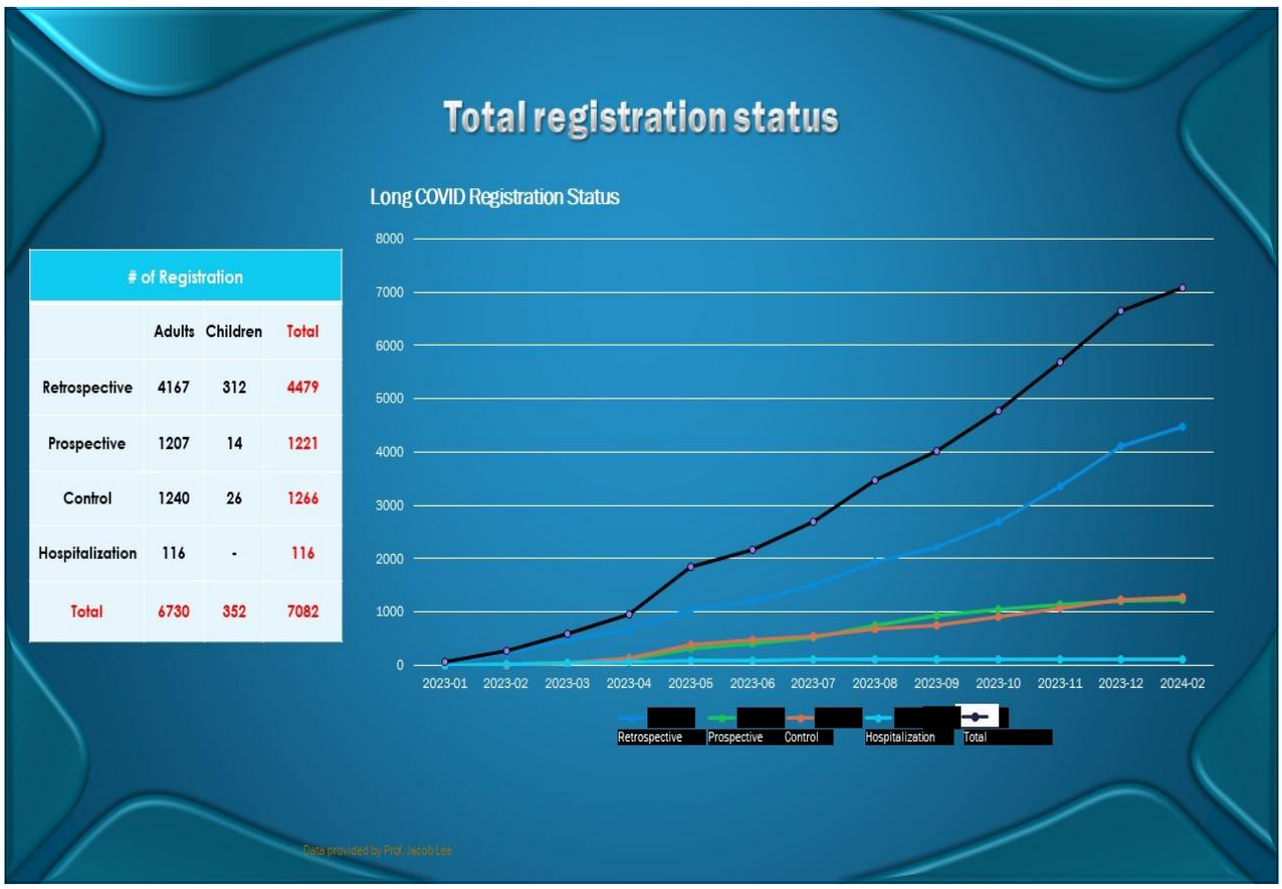
JAMA Intern Med. 2023 Mar 23 : e230743.


Korean Long COVID-19 Cohort
www.KOLOC.or.kr

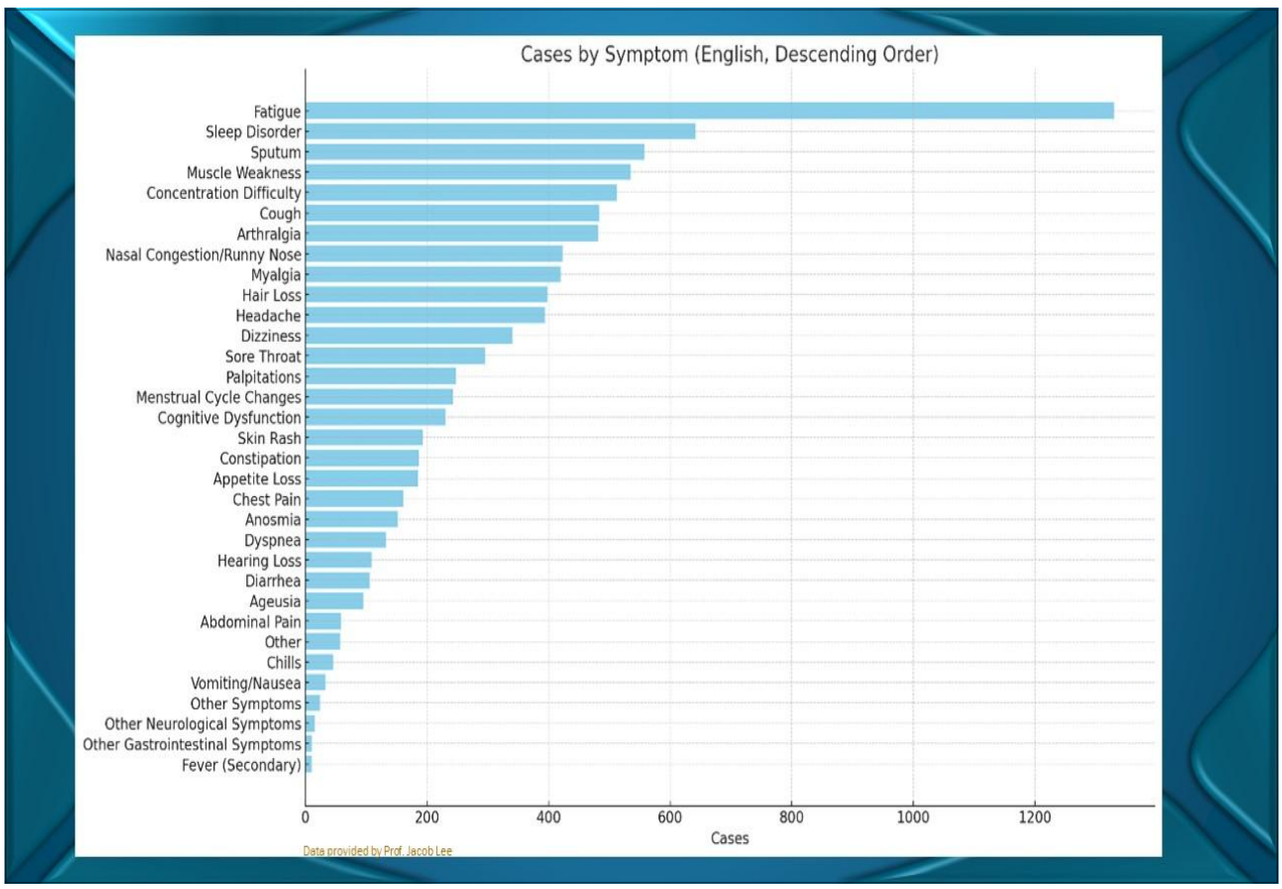

Chronic COVID-19 Syndrome Research and D evelopment Project in Korea
KDCA driven efforts to establish scientific evidence for identifying the causes and treatments of persistent symptoms following COVID-19 infection
Korea Disease Control Agency
Korea Health Industry Development Institute
Lead Research and Development Institution
(Prof. Jacob Lee, Hallym University)
Clinical-based post-COVID-19 sequelae patterns and guideline operation
Joint Research and Development Institution
(Prof. Jaehoon Jeong, Gachon University)
Research on Chronic COVID19 syndrome based on big data
Joint Research and Development Institution
(Prof. Seonghan Kim, Seoul Asan Hospital)
Translational research on Chronic COVID-19 syndrome
16 participating medical institutes
Research period: August 2022 – December 2025
Participation is possible regardless of COVID-19 diagnosis status.
KDCA press released 3 Jul 2023). 코로나19 예방접종, 코로나19감염 이후 주요질환발생 위험을 낮춰. Contents from original document was translated to English.

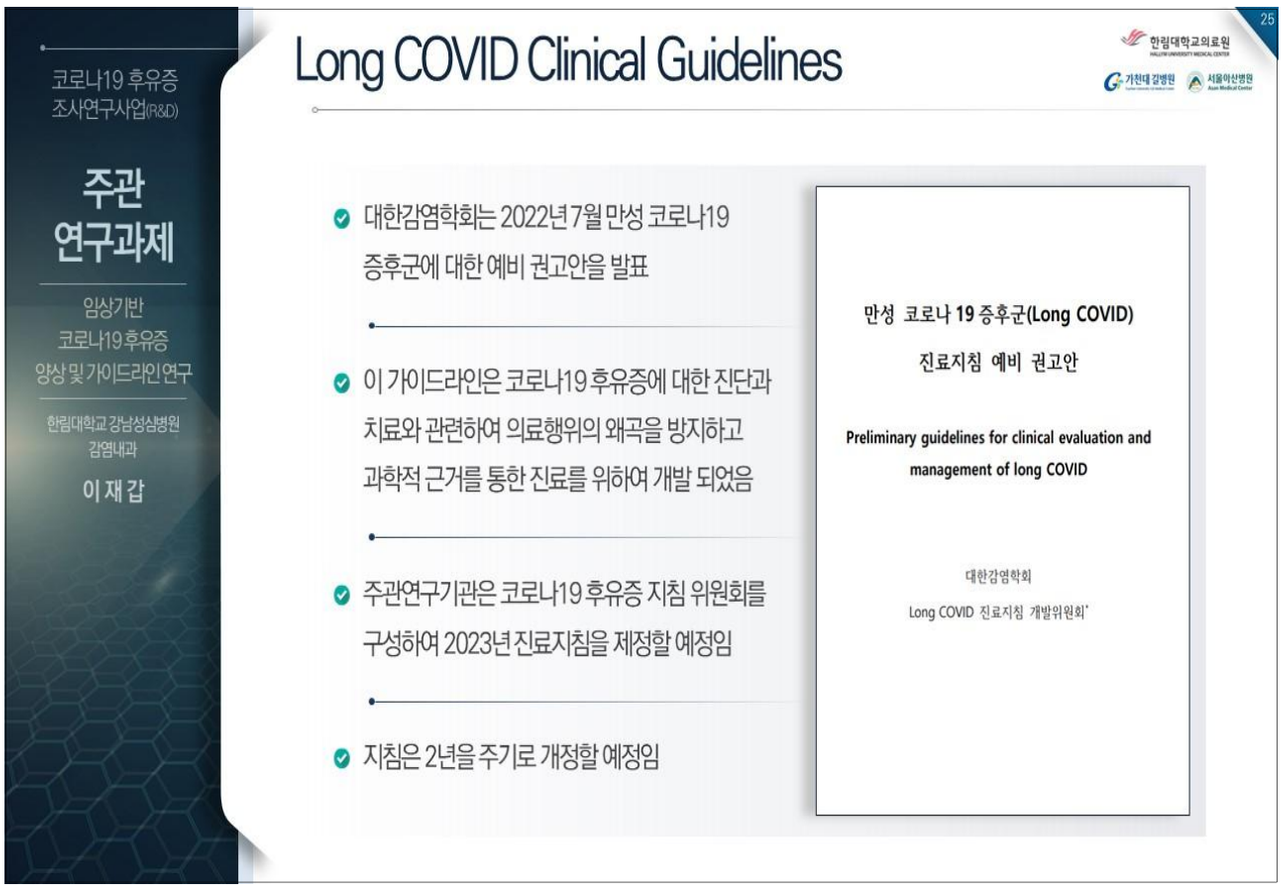

Future Strategies to expand Long COVID-19 management
Clinical-based Chronic COVID-19 syndrome patterns and guideline operation
• Establish and operate a cohort of COVID-19 cases, including children and adolescents, to investigate patterns of post COVID-19 syndrome and to provide treatment guidelines
*treatment guideline soon to be announced in Feb.
Research on Chronic COVID19 syndrome based on big data
• Establish a database of consent-based materials such as clinical research and translational research, and developing a platform for their utilization
Active promotion of the research projects to enroll participants partnering with Government and medical institutes
Translational research on Chronic COVID-19 syndrome
• Translational research to understand causes of chronic COVID-19 syndrome, identify biomarkers, and more
Long COVID19란?
코로나19 후유증 조사연구 대상자 모집
http://kolac.or.kr/frt/index.do

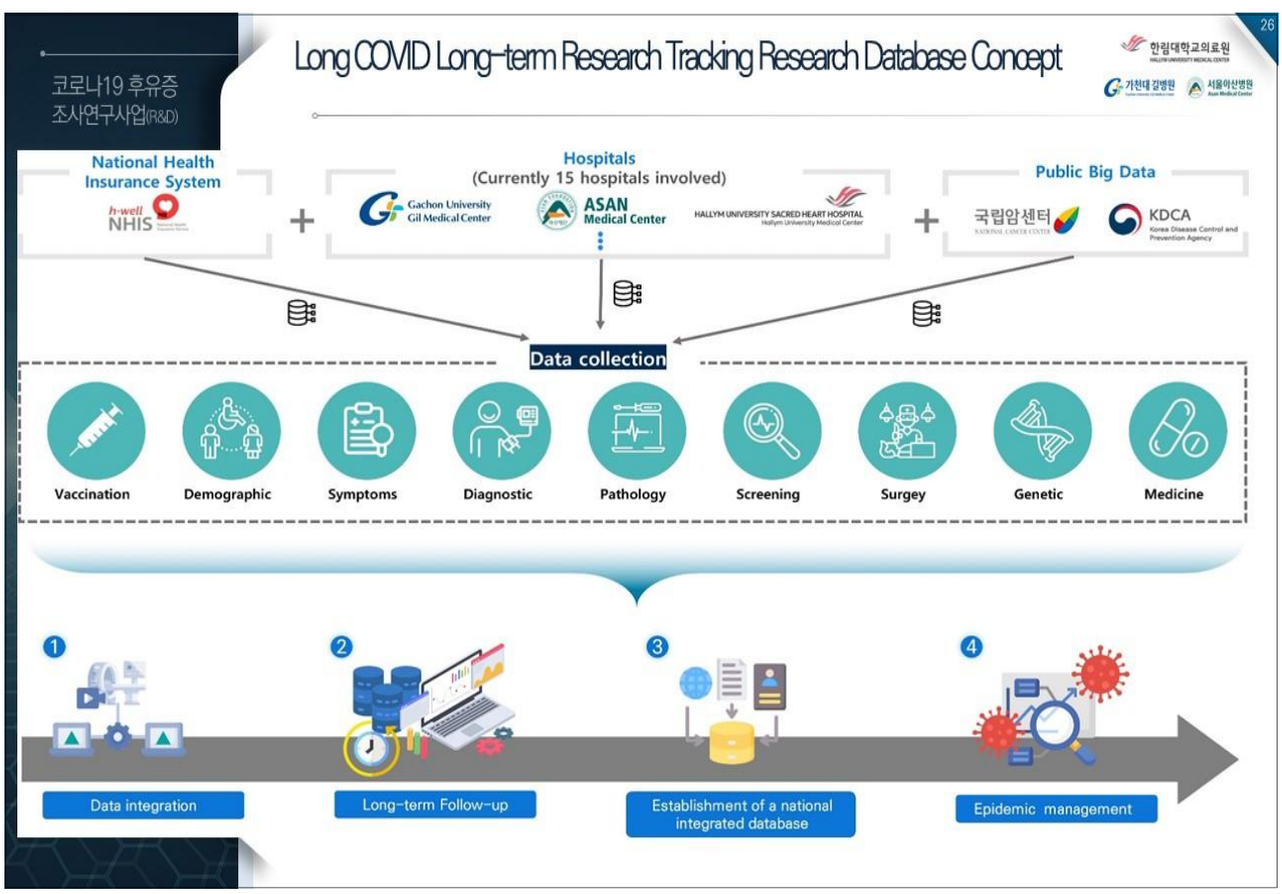

코로나19 후유증 조사연구사업(R&D)
주관 연구과제
임상기반 코로나19후유증 양상 및 가이드라인연구
한림대학교 강남성심병원 감염내과
이 재 갑
22
Long COVID Cohort Study in Korea
한림대학교의료원
가천대 길병원
서울아산병원
Retrospective and prospective
• 10,000
Prospective cohort
• 1,000
COVID-19-negative cohort
• 1,000
Inpatient/severe patient cohort
• 200



# of Registration			
	Adults	Children	Total
Retrospective	4167	312	4479
Prospective	1207	14	1221
Control	1240	26	1266
Hospitalization	116	-	116
Total	6730	352	7082



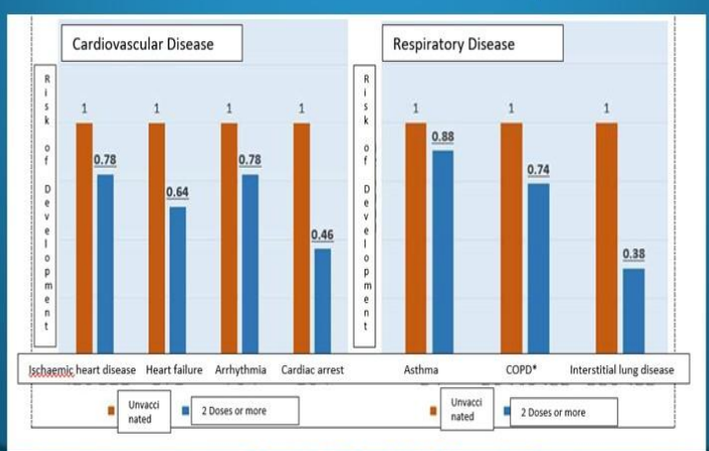

코로나19 후유증
조사연구사업(R&D)
주관
연구과제
임상기반
코로나19후유증
양상 및 가이드라인연구
한림대학교강남성심병원
감염내과
이 재 갑
Long COVID Clinical Guidelines
25
대한감염학회는 2022년 7월 만성 코로나19 증후군에 대한 예비 권고안을 발표
이 가이드라인은 코로나19 후유증에 대한 진단과 치료와 관련하여 의료행위의 왜곡을 방지하고 과학적 근거를 통한 진료를 위하여 개발 되었음
주관연구기관은 코로나19 후유증 지침 위원회를 구성하여 2023년 진료지침을 제정할 예정임
지침은 2년을 주기로 개정할 예정임
만성 코로나 19 증후군(Long COVID)
진료지침 예비 권고안
Preliminary guidelines for clinical evaluation and management of long COVID
대한감염학회
Long COVID 진료지침 개발위원회


코로나19 후유증
조사연구사업(R&D)
Long COVID Long-term Research Tracking Research Database Concept
26
National Health Insurance System
h-well NHIS
Hospitals
(Currently 15 hospitals involved)
Gachon University Gil Medical Center
ASAN Medical Center
HALLYM UNIVERSITY SACRED HEART HOSPITAL
Public Big Data
국립암센터
KDCA
Data collection
Vaccination
Demographic
Symptoms
Diagnostic
Pathology
Screening
Surgey
Genetic
Medicine
1
Data integration
2
Long-term Follow-up
3
Establishment of a national integrated database
4
Epidemic management

Interim analysis result of Post –COVID-19 syndrome using big data

- Design of study: 15 Jan 2022 to 15 Apr 2022. During the Omicron wave, 12,309,934 confirmed cases were observed for 4 months after the infection to compare the risk of 27 major diseases by vaccination status and number of doses.
- Outcomes. 1
  - Compared to the unvaccinated, those who have received two or more doses of vaccine have a reduced risk of cardiovascular disease, blood clots, kidney disease, respiratory disease, cirrhosis, diabetes, and other diseases after COVID-19 infection.

Risk Assessment: Association between COVID-19 vaccination and development of illness



KDCA press release(3 Jul 2023). 코로나19 예방접종 코로나19감염 이후 주요질환발생 위험률 낮춰. Contents from original document was translated to English.

Interim analysis result of Post –COVID-19 syndrome using big data

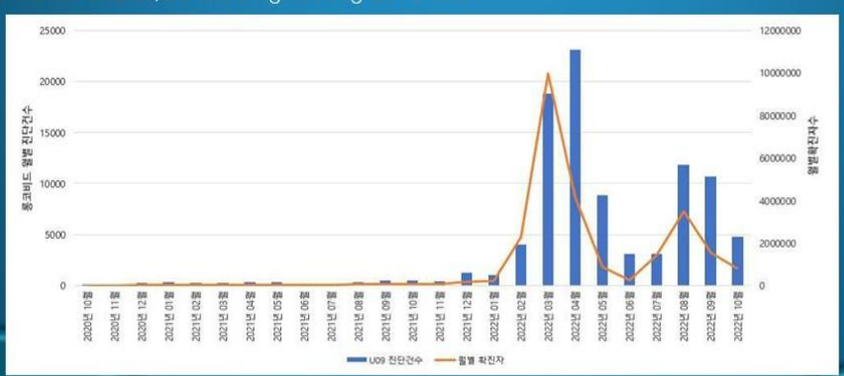
- Outcomes. 2
  - Those who received three doses were at a reduced risk of developing cardiovascular disease, kidney disease, etc. despite being more than 10 years older on average than those who received two doses.

Disease	Two doses	Three doses	Adjusted risk rate	P-value
Cardiovascular disease				
Heart Failure	1.28	2.51	0.85(0.77-0.93)	<.001
Arrhythmia	1.15	2.29	0.84 (0.76-0.93)	<.001
Cardiac arrest	0.31	0.62	0.73 (0.60-0.89)	0.002
Blood clot-related conditions				
Pulmonary embolism	0.55	0.86	0.79 (0.68-0.93)	0.004
Kidney Disease				
Dialysis	0.23	0.47	0.73 (0.57-0.92)	0.007
Liver Disease				
Acute Pancreatitis	0.82	1.03	0.87 (0.76-0.99)	0.04

KDCA press release(3 Jul 2023). 코로나19 예방접종 코로나19감염 이후 주요질환발생 위험률 낮춰. Contents from original document was translated to English.

Analysis using chronic COVID-19 syndrome diagnosis codes

- Design of study: Oct 2020 – Oct 2022. Notable aspects of cases diagnosed with U09 [post-COVID-19 syndrome] in Korea
- Outcomes:
  - (Overall and gender breakdown) Total patients 94,393, outpatient 91,593, inpatient 3,059
  - Incidence rates are higher in women [0.47%] than men [0.34%]
  - (Age) Higher incidence rates in older age groups (60+)
  - Incidence rate is almost 8 times higher for those aged 60+ at 0.87% compared to 0.11% for those under 10 years old
  - (Monthly) Highest long-covid cases detected immediately following the Omicron wave (23,112). One-month gap betwe en the Omicron BA.1/2 and the highest long-Covid cases.



KDCA press release(3 Jul 2023). 코로나19 예방접종, 코로나19감염 이후 주요질환발생 위험을 보춰. Contents from original document was translated to English.

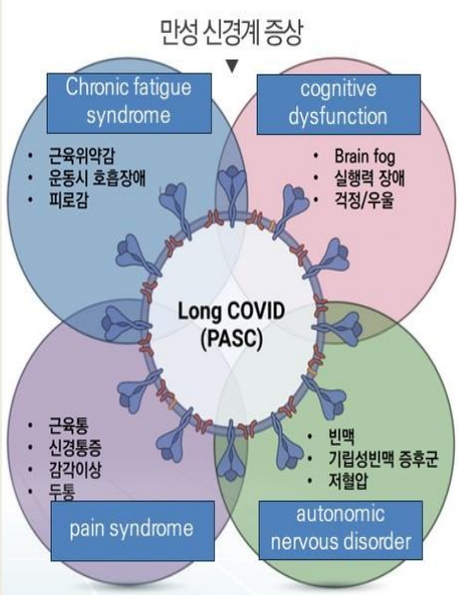
코로나19 후유증

COVID19 and chronic neurological symptoms

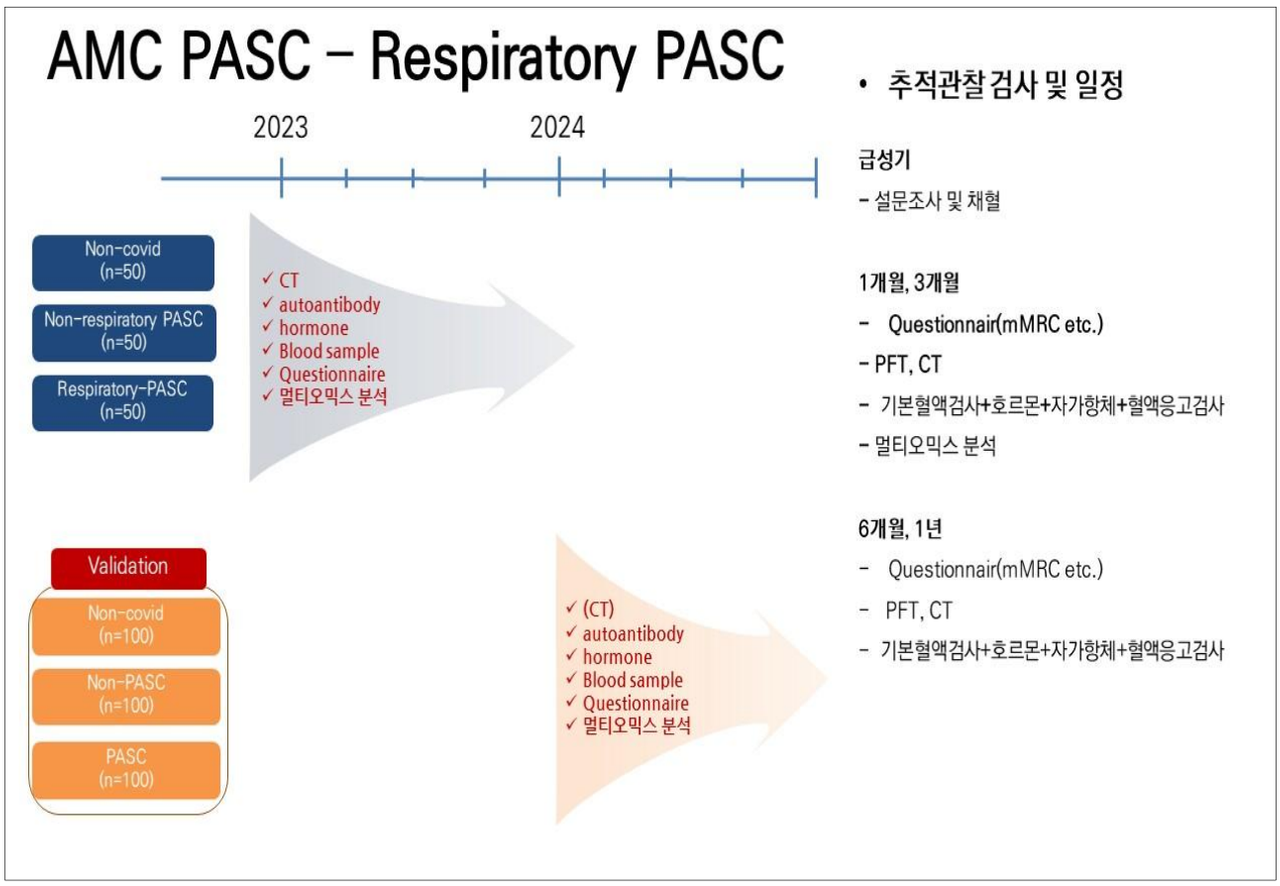
30

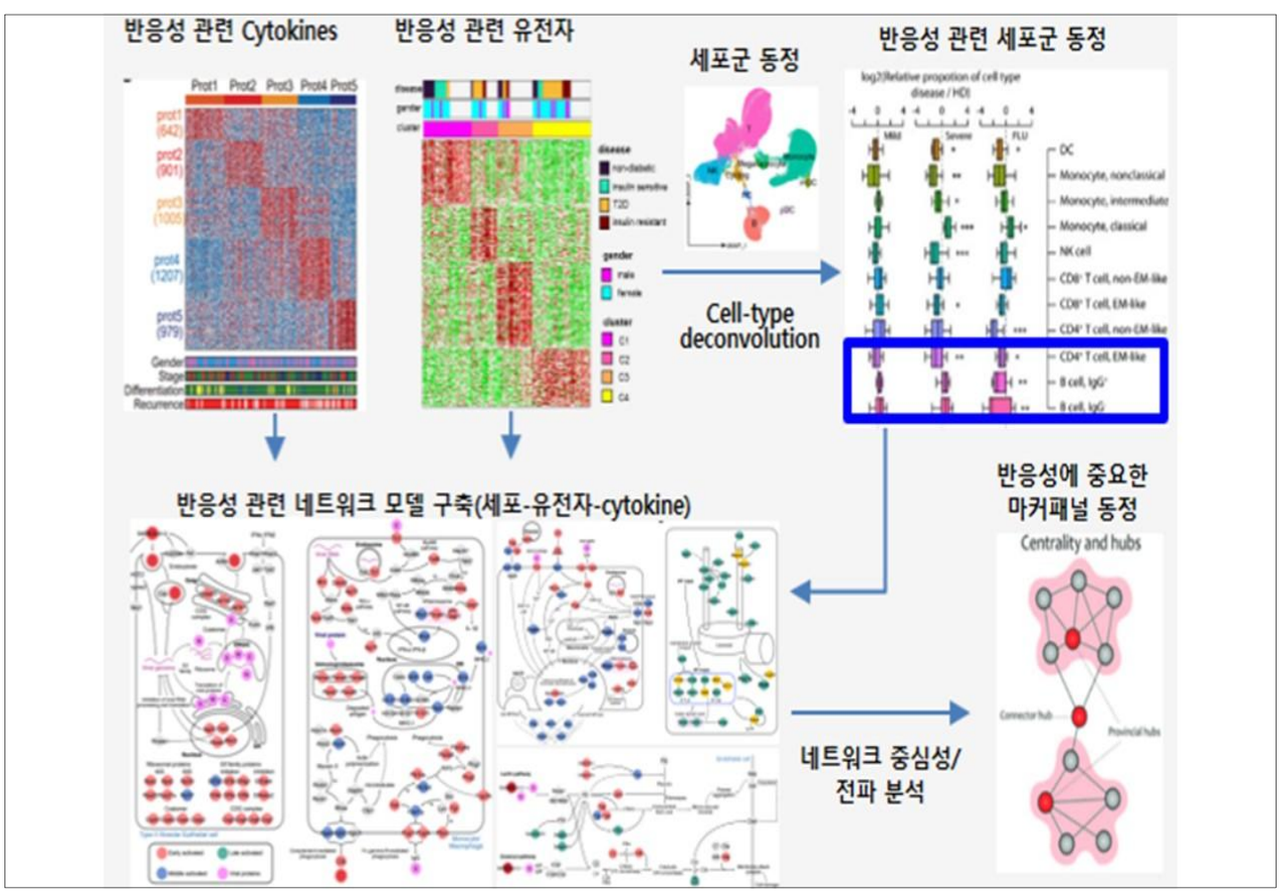
한림대학교의료원 HALLYM UNIVERSITY MEDICAL CENTER
가천대 길병원 서울아산병원 Asan Medical Center

- Chronic neurological symptoms are commonly reported as a sequelae of COVID19 (~20%)
- Chronic fatigue and cognitive decline are the main symptoms, and they have a significant impact on quality of life. → Management such as prevention and treatment is urgently needed in COVID19 patients.
- The pathophysiology is not yet known, and it can occur even in patients who had no acute symptoms, especially in the acute phase. → Disease monitoring biomarkers are needed to identify the mechanism of occurrence and identify risk groups.

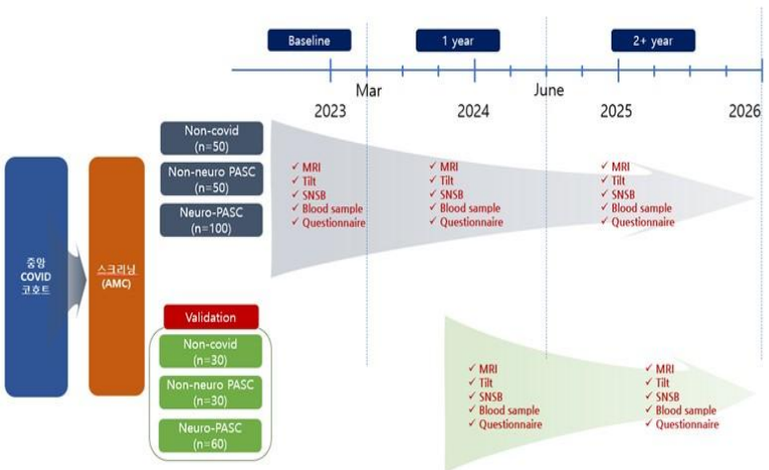


Brain, 2021


AMC PASC – Respiratory PASC
2023
2024
Non-covid (n=50)
Non-respiratory PASC (n=50)
Respiratory-PASC (n=50)
✓ CT
✓ autoantibody
✓ hormone
✓ Blood sample
✓ Questionnaire
✓ 멀티오믹스 분석
Validation
Non-covid (n=100)
Non-PASC (n=100)
PASC (n=100)
✓ (CT)
✓ autoantibody
✓ hormone
✓ Blood sample
✓ Questionnaire
✓ 멀티오믹스 분석
• 추적관찰 검사 및 일정
급성기
- 설문조사 및 채혈
1개월, 3개월
- Questionnair(mMRC etc.)
- PFT, CT
- 기본혈액검사+호르몬+자가항체+혈액응고검사
- 멀티오믹스 분석
6개월, 1년
- Questionnair(mMRC etc.)
- PFT, CT
- 기본혈액검사+호르몬+자가항체+혈액응고검사


반응성 관련 Cytokines
반응성 관련 유전자
세포군 동정
반응성 관련 세포군 동정
Cell-type deconvolution
반응성 관련 네트워크 모델 구축(세포-유전자-cytokine)
반응성에 중요한 마커패널 동정
Centrality and hubs
네트워크 중심성/ 전파 분석

AMC – Neurologic PASC



- **추적관찰 검사 및 일정**

스크리닝(Neuro-PASC)

- 인지기능과 피로도 조사(간단한 설문)

3개월 주기

- 증상변수(피로도): FAS 및 DSQ-SF
- Neuro-PASC 관련 여러 신경학적 증상(설문)
  : 어지럼, 걱정(anxiety), 우울, 수면, 삶의 질 등

6개월 주기

- 혈액 검사(혈액 바이오마커 분석 용도)

1년 주기

- 증상변수(인지기능): 신경심리검사(SNSB)
- 중추신경계 뇌 영상(Brain MRI)
- 자율신경계검사(Tilt table)

Conclusion

- The COVID-19 pandemic is the worst pandemic of the 21st century
- COVID-19 is not simply an infection that ends with recovery, but is causing long-term sequelae.
- Korea is conducting research on a long COVID cohort by providing large-scale research funds led by the government.
- Currently, 4,500 cohort members have been registered and the epidemiological data of patients will be analyzed
- Joint research institutions are conducting research through big data-based analysis and translational research

세션 2.
신종감염병 치료제개발 현황 및 전략

2024
감염병연구기관 국제심포지엄
International Symposium for Infectious Diseases Research Institutes Cooperation

Chair

Ki-Soon Kim

- Institute of Viral Disease Department of Microbiology, College of Medicine, Korea University
- Professor

EDUCATION:

- 2000 Ph.D. / Department of Life Science, College of Natural Science, Chung-Ang University
- 1990 M.S. / Department of Biology, College of Natural Science, Korea University Graduate School
- 1988 B.S. / Department of Biology, College of Natural Science, Korea University

PROFESSIONAL EXPERIENCE:

- 2022 ~ Present Advisory member of Infectious Disease Policy Beauro, Seoul Metropolitan city, Korea
- 2022 ~ Present Committee member of Government-wide R&D Fund for Infectious Disease Research (GFID), Korea
- 2021 ~ Present Advisory member of Korea Pest Control Association, Korea
- 2020 ~ Present Committee member of Bureau of Infectious Disease Policy, KCDA, Korea
- 2006 ~ Present Lifetime member, The American Society of Virology
- 1990 ~ Present Committee member, The Korean Society of Virology
- 1990 ~ 2019 Director, Researcher, Divisions of Influenza and respiratory viruses, Department of Virus Research, National Institute of Health, Korea
- 2004 ~ 2006 University of Nebraska Medical Center, NE, USA, Visiting Scientist
- 1996 ~ 1997 Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan, Visiting Scientist
- 1994 ~ 1994 NIID, Tokyo, Japan, “Polio Eradication Program”, WHO fellow

01

신속 팬데믹 대응을 위한 플랫폼과 기술들

Dimitri LAVILLETTE
한국파스퇴르연구소

Speaker

Dimitri LAVILLETTE

- Institut Pasteur Korea
- Chief Scientific Officer

EDUCATION:

- 2009 Dr Habil, Habilitation à diriger les recherches (HDR), ENS Lyon, France
- 2000 PhD in Virology, University Claude Bernard Lyon1/ Ecole Normale Supérieure, Lyon, France
- 1997 D.E.A of Differentiation, Genetic and Immunology, University Claude Bernard, Lyon, France

PROFESSIONAL EXPERIENCE:

- 2022 ~ Present Institut Pasteur Korea, Chief Scientific Officer, Korea
- 2014 ~ 2022 Institut Pasteur of Shanghai – Chinese Academy of Sciences, Principal Investigator and Professor, China
- 2012 ~ 2014 Claude Bernard Lyon 1 University, Associate Professor (2012-2014) UMR 5557 CNRS INRA VetAgroSup, Microbial Ecology
- 2011 Glycobiology Institute, Visiting scientist; Oxford, U.K.
- 2003 ~ 2012 ENS Lyon, INSERM U758, Human virology, Associate Professor, France
- 2003 ~ Present National Center of Scientific Research (CNRS), Tenure staff scientist position CR1; France
- 2001 ~ 2003 Oregon Health Sciences University, Post Doc. Oregon, U.S.A
- 2000 ~ 2001 Mayo Clinic, Visiting scientist Rochester, MN, U.S.A.

Topic

Platforms & Tools to Enable Rapid Pandemic Response

Abstract

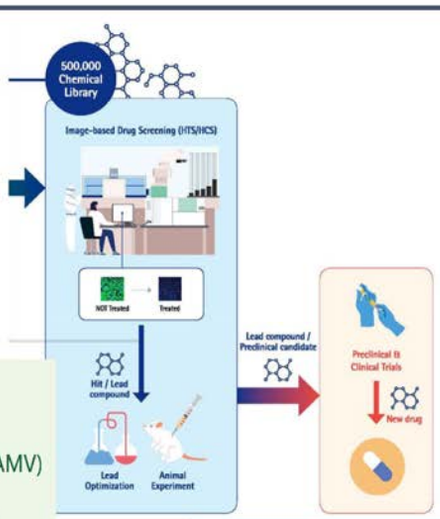
The recent COVID-19 pandemic has caused economic and social damage worldwide and gives us considerable concerns about a new pandemic in the future. Unlike other diseases, infectious diseases are very difficult to prepare for, and they quickly begin to spread around the world before humanity prepares in advance. Due to this, it is very difficult to fight a new strain of virus that appears quickly and spreads rapidly by the method of developing a general treatment applied to other diseases. A strategy for the development of potential treatments by families of pathogens, using prototypes, can be implemented following different priorities of different agencies. Infectious diseases progress through the process of infection, spread and pathogenicity. Strategic approaches of treatment are applied for each stage of progression. Therapeutic agents such as monoclonal antibodies or variable domains of heavy-chain antibodies (VHH) being used for inhibiting infection, and small compound inhibitory agents of viral replication are being used as therapeutic agents that prevent the spread or amplification of pathogens after infection. In addition, agents to control immune response against the pathogenesis are being applied as therapeutics for infectious diseases to reduce the severity and fatality rate. The prevention strategies with the elaboration of vaccines are dramatically increasing as well. This presentation will discuss the development strategies against infectious diseases that are investigated in the Institut Pasteur Korea such as VHH derived from camelids and antiviral drugs in a preparedness program.

Platforms & Tools to Enable Rapid Pandemic Response

Dimitri LAVILLETTE, PhD, Dr. Habil
Chief Scientific Officer Institut Pasteur Korea

Dimitri.Lavillette@ip-korea.org

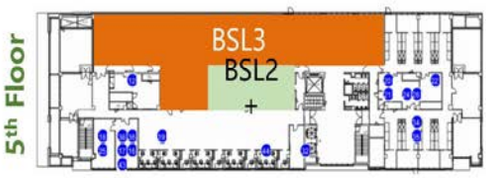
IPK's Drug Discovery Approach



Research teams
- **Zoonotic Virus** (ZVL)
- **Viral Immunology** (VIL)
- **Applied Molecular Virology** (AMV)
- **Tuberculosis** (TRL)
- **Antibacterial Resistance** (ARL)
- **Host-Parasite** (HPRL)
- **Advanced Biomedical** (ABRL)

Research teams
- **Screening Discovery** (SDP)
- **Bioinformatics & Data Analysis** (BDA)
- **Medicinal Chemistry** (MC)
- **Animal Research Lab** (ANL)
- **Technology Development** (TDP)
- **BioBank** (BBK)

IPK Drug Screening Platform



Biological Safety Level 3
- HCS: Confocal mode >10,000 pts/day
- Multi-label Reader: >20,000 pts/day

Biological Safety Level 2+
- HCS: Confocal mode >20,000 pts/day
- Multilabel Reader: >25,000 pts/day

Biochemical
- Multi-label Reader: >20,000 pts/day

Chemical Library

[IPK Diversity sets]
IPK Legacy: ~ 230K
IPK 2015:~ 100K
IPK MedChem: ~ 9.5K

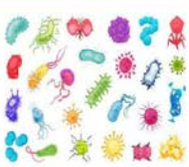
[IPK Pilot]
Drugs &
Bioactives: ~ 12K

[IPK Natural Products]
NCI Collections: ~ 150K

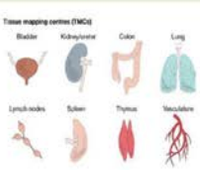
RESPONSIVENESS : Task Force rapidly mobilizable, available people/reagents/models

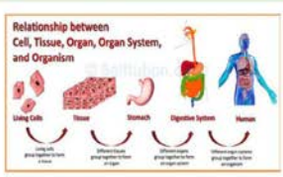
What do we need to prepare for the next outbreak to do drug screening rapidly?

1. Pathogen Access

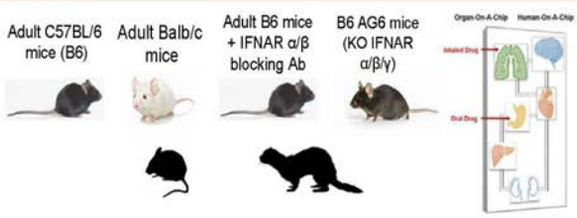


2. Cell lines

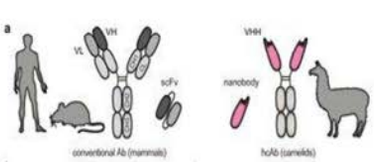




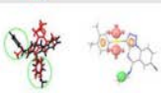
3. Animal Models



4. Detection



5. Drug Library



6. Trained team, infrastructures and funds

Threat: During outbreak, regular channels, collaborators, close doors "lockdown" prevent delivery of reagents...
Need to secure relative independance

RESPONSIVENESS : Task Force rapidly mobilizable, available people/reagents/models

What do we need to prepare for the next outbreak to do drug screening rapidly?

1. Pathogen Access

Secure collaborative channels (Pasteur Network)
Secure regulations (Nagoya protocol, Korea - Biosafety team)

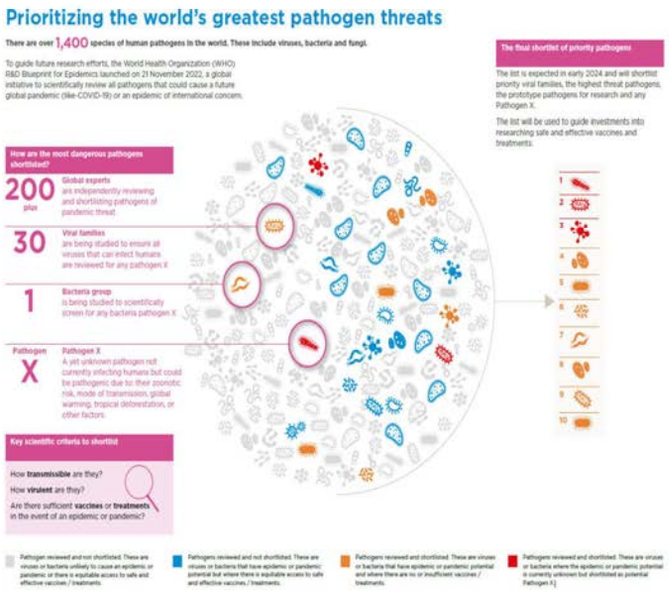
Development of molecular clones (virus)

Biobank Import "prototypes" for different family of pathogens

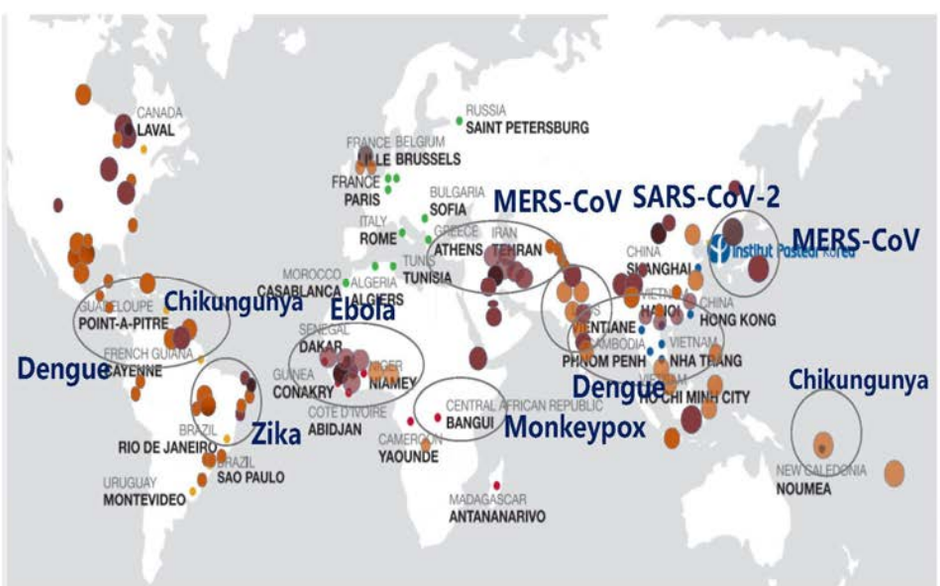
GISB 글로벌감염병연구자원은행 Global Infectious Disease Specimen Bank

GISB mail? Website?

Pathogens Biobank IPK
Liquid Nitrogen freezer room



Pasteur Network Ideally positioned at the frontline of outbreaks



Collaboration with **Institut Pasteur de Dakar**

Barkedji

Close to a pond

CDC trap

Mosquitoes sorting after field collection

Dir Amadou SALL Virology team

Kedougou

Close to a river

Larvae collection from a « trou de roche »

A*edes aegypti collected* on the field sorting

Students involved in the work

Try to go beyond the WHO' s R&D Blueprint virus disease priority list

7

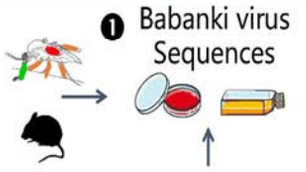
RESPONSIVENESS : Task Force rapidly mobilizable, available people/reagents/models

What do we need to prepare for the next outbreak to do drug screening rapidly?

1. Pathogen Access

❶ Babanki virus Sequences

Synthetic genes



Virus isolation (Institut Pasteur Dakar, Senegal)

❷ **Molecular tools**

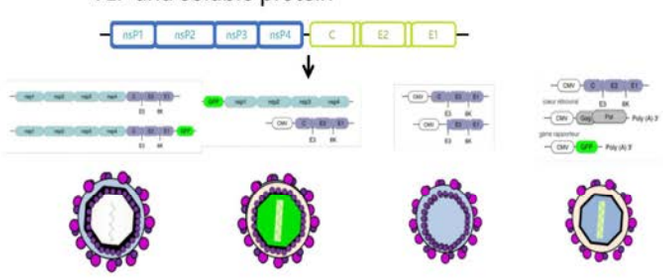
- Replicating virus

.Infectious clone (full length or ISA)

.Tagged replicating virus

_ Non replicative « virus » (RVP, PP)

- VLP and soluble protein

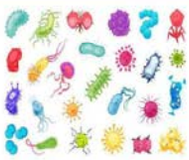


	Molecular clone Native or tagged virus	Reporter virus Particules (RVP)	Virus Like Particles (VLP)	Retroviral Pseudoparticles (PP)
Biosecurity:	Level 3	Level 2	Level 2	Level 2
Production:	Difficult	Quick, (flexible)	Quick, (flexible)	Easy, quick, flexible
Immunogenicity:	wt	wt	wt	(wt)

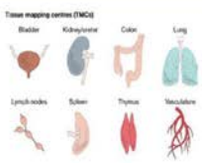
RESPONSIVENESS : Task Force rapidly mobilizable, available people/reagents/models

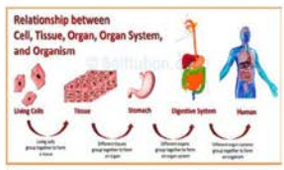
What do we need to prepare for the next outbreak to do drug screening rapidly?

1. Pathogen Access

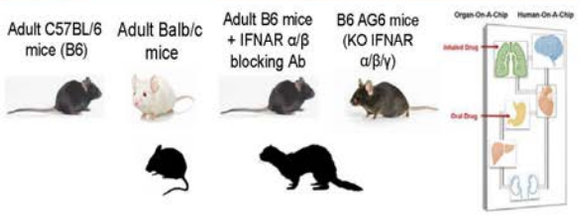


2. Cell lines





3. Animal Models



RESPONSIVENESS : Task Force rapidly mobilizable, available people/reagents/models

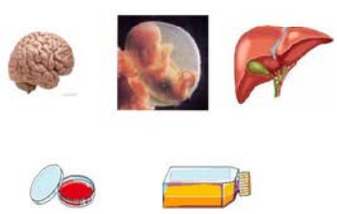
What do we need to prepare for the next outbreak to do drug screening rapidly?

2. Cell lines

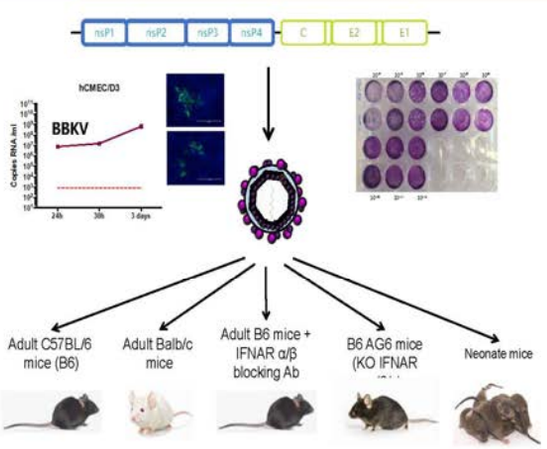
Risk Assessment Studies:

Tropism and Pathogenesis

Vector Competence



3. Animal Models



Risk Assessment Studies:

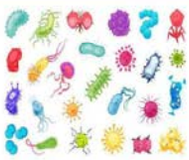
Tropism and Pathogenesis

Vector Competence

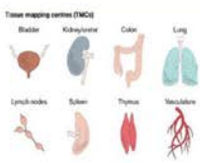
RESPONSIVENESS : Task Force rapidly mobilizable, available people/reagents/models

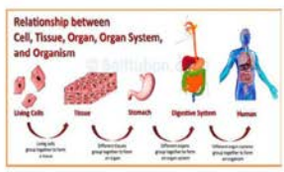
What do we need to prepare for the next outbreak to do drug screening rapidly?

1. Pathogen Access

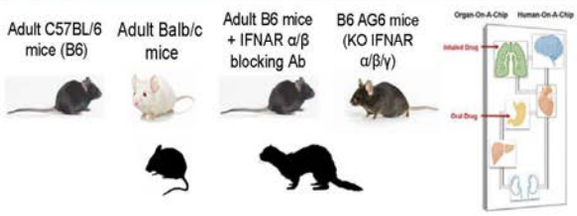


2. Cell lines

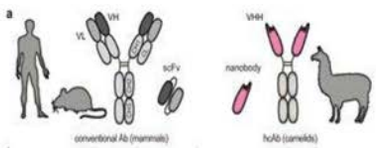




3. Animal Models



4. Detection

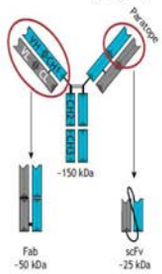


Objective

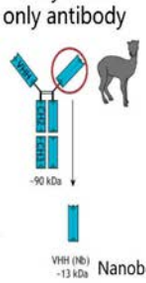
Antibody development platforms

Antibody development considerations: Time, cost; diversity, affinity...

Conventional antibody (IgG)



Heavy chain-only antibody



Nanobody®

In vitro platform

1.Library screening

Synthetic nanobody; naïve human Ab library

2.Engineer related antibody

Potential coronavirus nAb.
Mutation, bispecific, multivalence, appendant...

3.Optimization platform

Phage display, affinity maturation...

Fast, low cost, easy manipulation.

In vivo immunization

1.Convalescent human

(Or vaccinated).
Specific B cell cDNA; single B cell sorting.

2.Rodent immunization

Hybridoma; humanized mouse

3.Immunization of others

Llama/Alpaca - nanobody

Somatic hypermutation, V(D)J recombination.

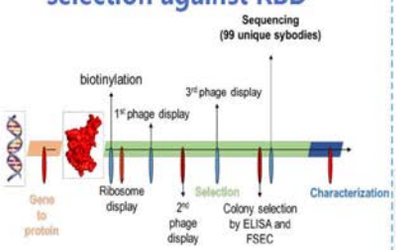
12

Conclusion

Development of neutralizing nanobodies and human monoclonal antibodies.

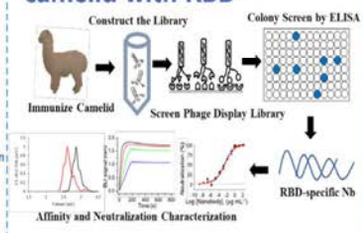
We reported different antibodies (MR3-Fc, DL4, DL28, FD20 and Ab08) against SARS-CoV-2 isolated using RBD, and they show good neutralizing potential.

Synthetic nanobody selection against RBD



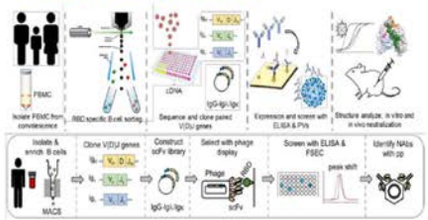
100 sybodies in 12 days

Usual route for nanobody discovery by immunizing camelid with RBD



28 nanobodies in 3 months

Human monoclonal antibody isolated from convalescent of COVID-19 patients



1 mAb in 2 months,
1 mAb in 1.5 months

Li T, Zhou B, Luo Z, Lai Y, Huang S, Zhou Y, Li Y, Gautam A, Bourgeau S, Wang S, Bao J, Tan J, **Lavillette D***, Li D*. **Front Microbiol.** 2022 Jun 2;13:875840. doi: 10.3389/fmicb.2022.875840

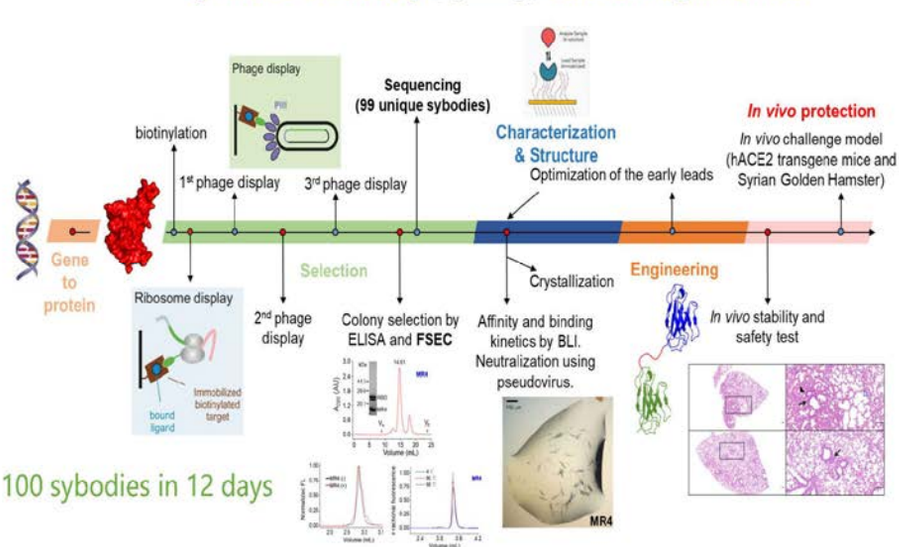
A Spike-destructing human antibody effectively neutralizes Omicron-included SARS-CoV-2 variants with therapeutic efficacy. Meng L, Zha J, Zhou B, Cao L, Jiang C, Zhu Y, Li T, Lu L, Zhang J, Yang H, Feng J, Gu Z, Tang H, Jiang L, Li D, **Lavillette D***, Zhang X*. **PLoS Pathog**. 2023 Jan 27;19(1):e1011085. doi: 10.1371/journal.ppat.1011085

13

Results

Nanobody : *FAST*, low cost, stable

Synthetic nanobody (Sybody) selection against RBD



100 sybodies in 12 days

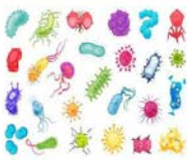
Markus Seeger, Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland.
Nature Protocols volume 15, pages1707–1741 (2020)

14

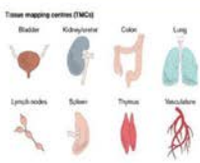
RESPONSIVENESS : Task Force rapidly mobilizable, available people/reagents/models

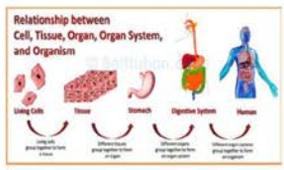
What do we need to prepare for the next outbreak to do drug screening rapidly?

1. Pathogen Access

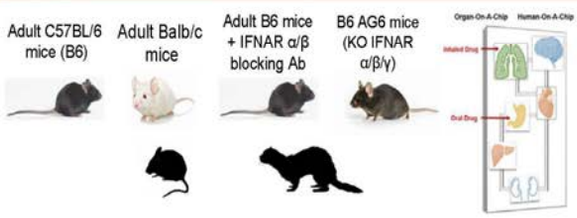


2. Cell lines

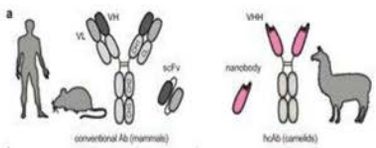




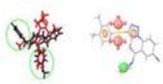
3. Animal Models



4. Detection



5. Drug Library

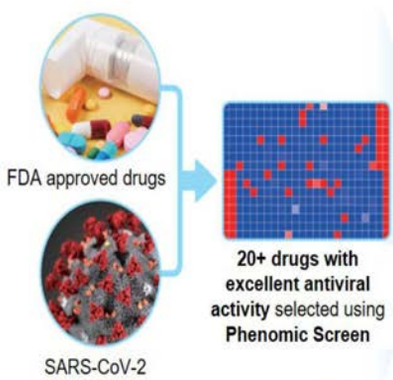


6. Trained team, infrastructures and funds

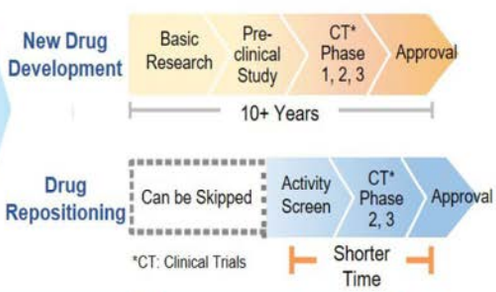
Threat: During outbreak, regular channels, collaborators, close doors "lockdown" prevent delivery of reagents...
Need to secure relative independance

Drug Repositioning Strategy @ IPK

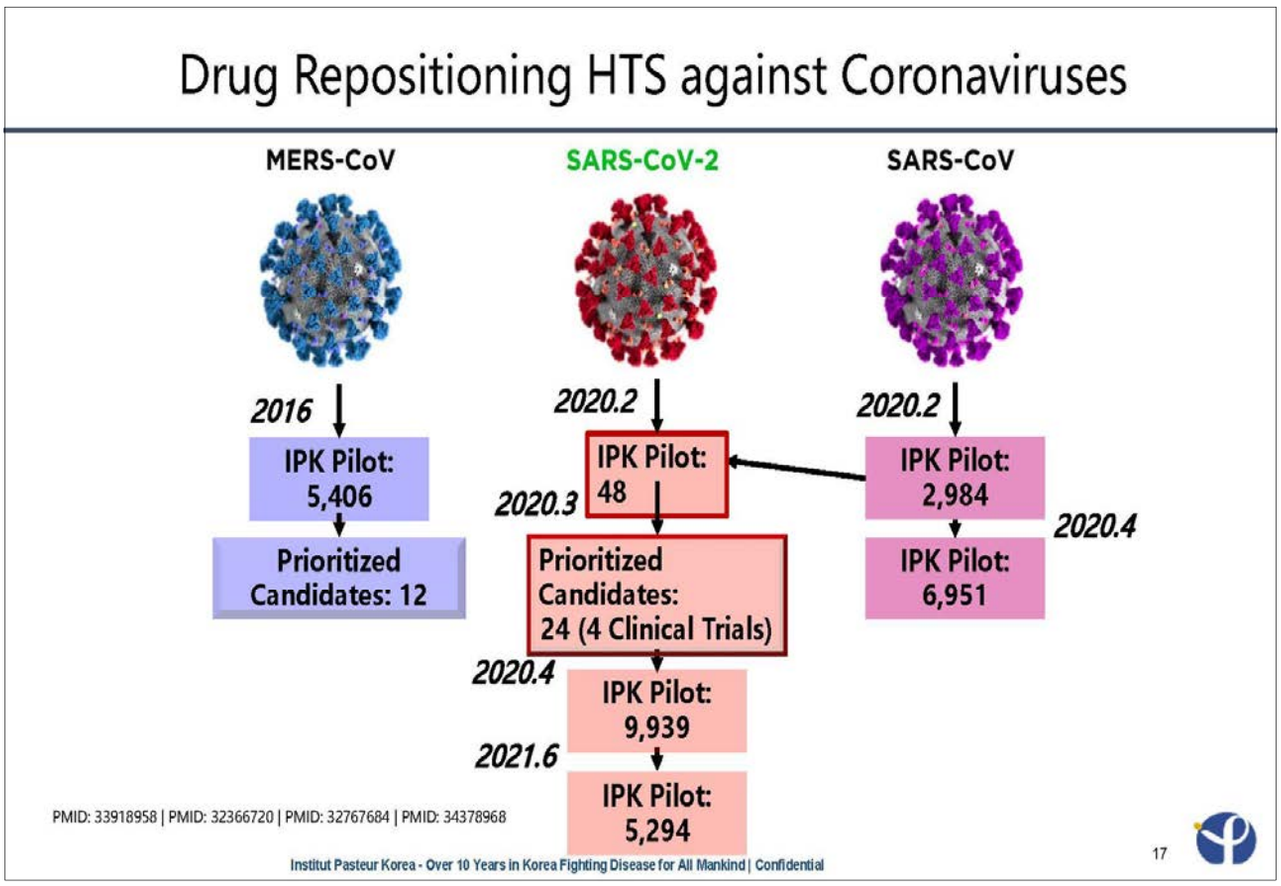
IPK PILOT LIBRARY (Small Molecule): Approved, Investigational, Bioactives, Natural Products

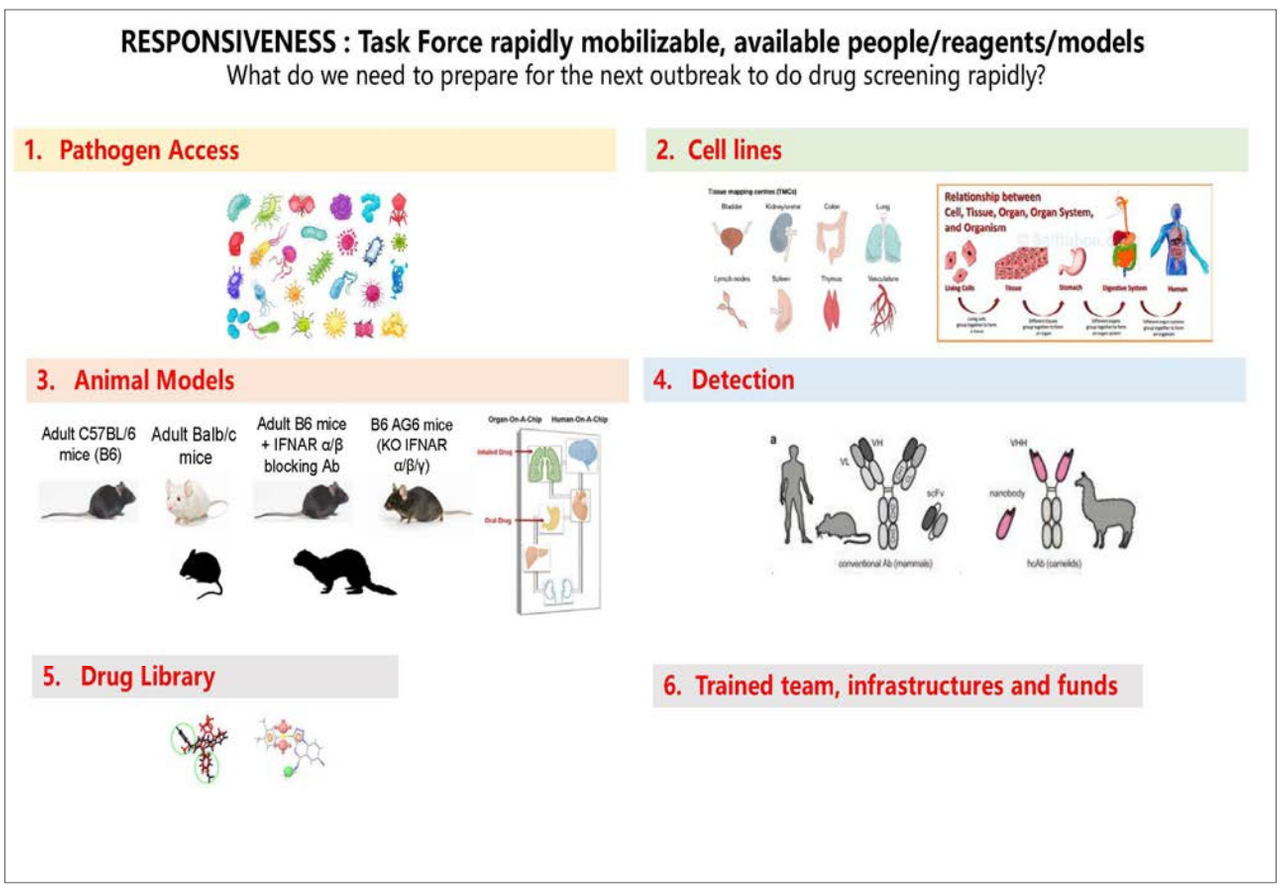


The BEST strategy
to develop COVID-19 treatment
in a short time



Institut Pasteur Korea - Over 10 Years in Korea Fighting Disease for All Mankind | Confidential


Drug Repositioning HTS against Coronaviruses
MERS-CoV
SARS-CoV-2
SARS-CoV
2016
IPK Pilot: 5,406
Prioritized Candidates: 12
2020.2
IPK Pilot: 48
2020.3
Prioritized Candidates: 24 (4 Clinical Trials)
2020.4
IPK Pilot: 9,939
2021.6
IPK Pilot: 5,294
2020.2
IPK Pilot: 2,984
2020.4
IPK Pilot: 6,951
PMID: 33918958 | PMID: 32366720 | PMID: 32767684 | PMID: 34378968
Institut Pasteur Korea - Over 10 Years in Korea Fighting Disease for All Mankind | Confidential
17


RESPONSIVENESS : Task Force rapidly mobilizable, available people/reagents/models
What do we need to prepare for the next outbreak to do drug screening rapidly?
1. Pathogen Access
2. Cell lines
Relationship between Cell, Tissue, Organ, Organ System, and Organism
3. Animal Models
Adult C57BL/6 mice (B6)
Adult Balb/c mice
Adult B6 mice + IFNAR α/β blocking Ab
B6 AG6 mice (KO IFNAR α/β/γ)
4. Detection
5. Drug Library
6. Trained team, infrastructures and funds

Expanding and Operating (A)BSL-3 Open Labs
> Research Resource Center (RRC)

Purpose	**Establish core research infrastructure facilitating basic research on infectious disease** **Operate as metropolitan open labs & support scientific community**
Major facility	**1 Biosafety Level 3 facility** (249.27㎡, 4 laboratories, 1 equipment room) **1 Animal Biosafety Level 3 facility** (328.39㎡ 2 breeding rooms, 3 laboratories, 2 autopsy rooms) **1 Biobank** (148.79㎡, 2 storage rooms, 3 laboratories)
Budget	**Approx. 16.9 billion KRW (9.8 billion KRW in 2022) by MSIT**
Period	**2021~2023 (3 years)**

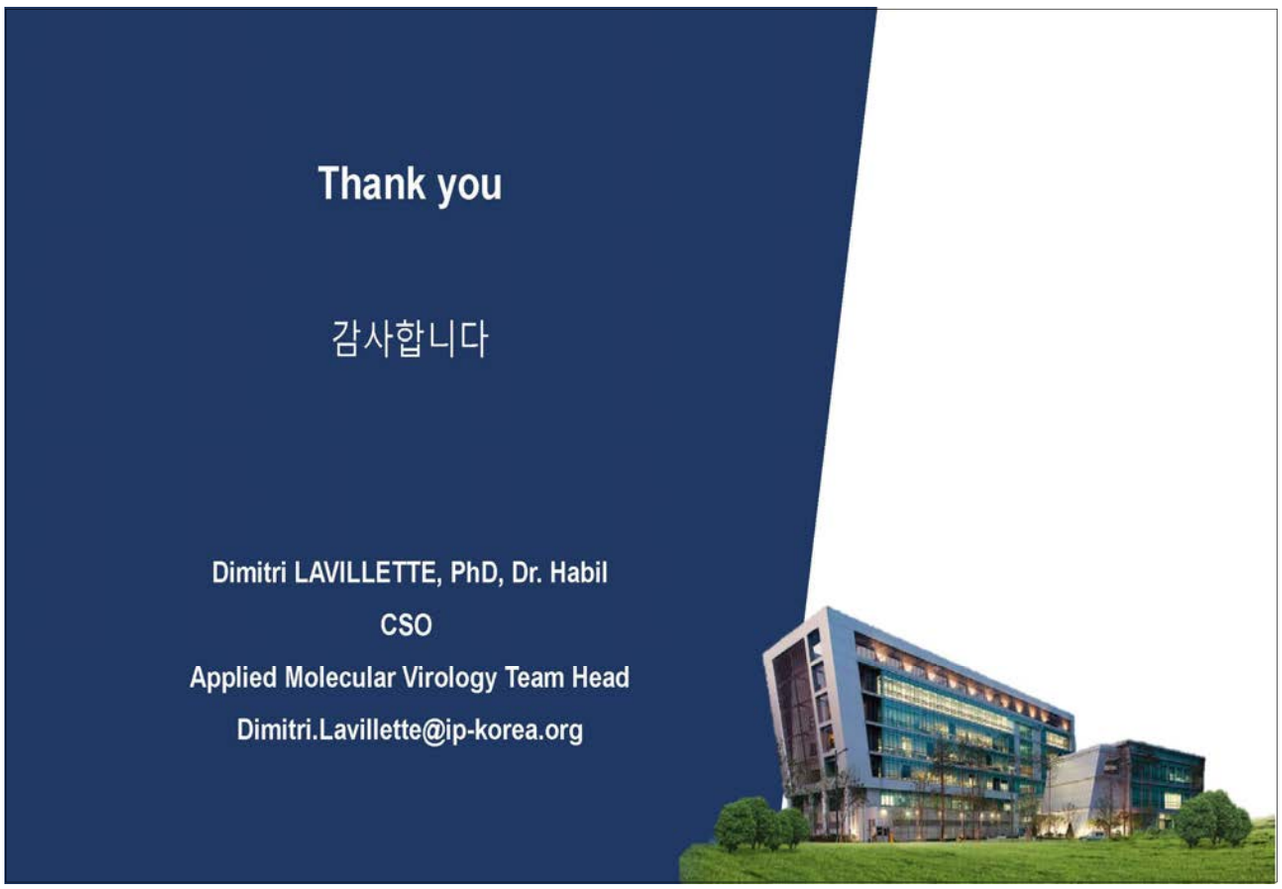
(Total 1,688m²(511py))

Expanding and Operating (A)BSL-3 Open Labs
> Research Resource Center (RRC)

Plan	**- Establish operation of IACUC.** **- Kick-off meeting hold in October 2023.**

https://rrc.ip-korea.org

Mail: RRCS_Team@ip-korea.org


Thank you
감사합니다
Dimitri LAVILLETTE, PhD, Dr. Habil
CSO
Applied Molecular Virology Team Head
Dimitri.Lavillette@ip-korea.org

02

SARS-CoV-2 S2 타켓 백신 및 치료항제 개발

조은위 센터장
한국생명공학연구원

Speaker

Cho, Eun-Wie

- Korea Research Institute of Bioscience and Biotechnology (KRIBB)
- Principal Researcher

EDUCATION:

- 2001 Ph.D in Biological Science, Korea Advanced Institute of Science & Technology (KAIST), Biological Science

PROFESSIONAL EXPERIENCE:

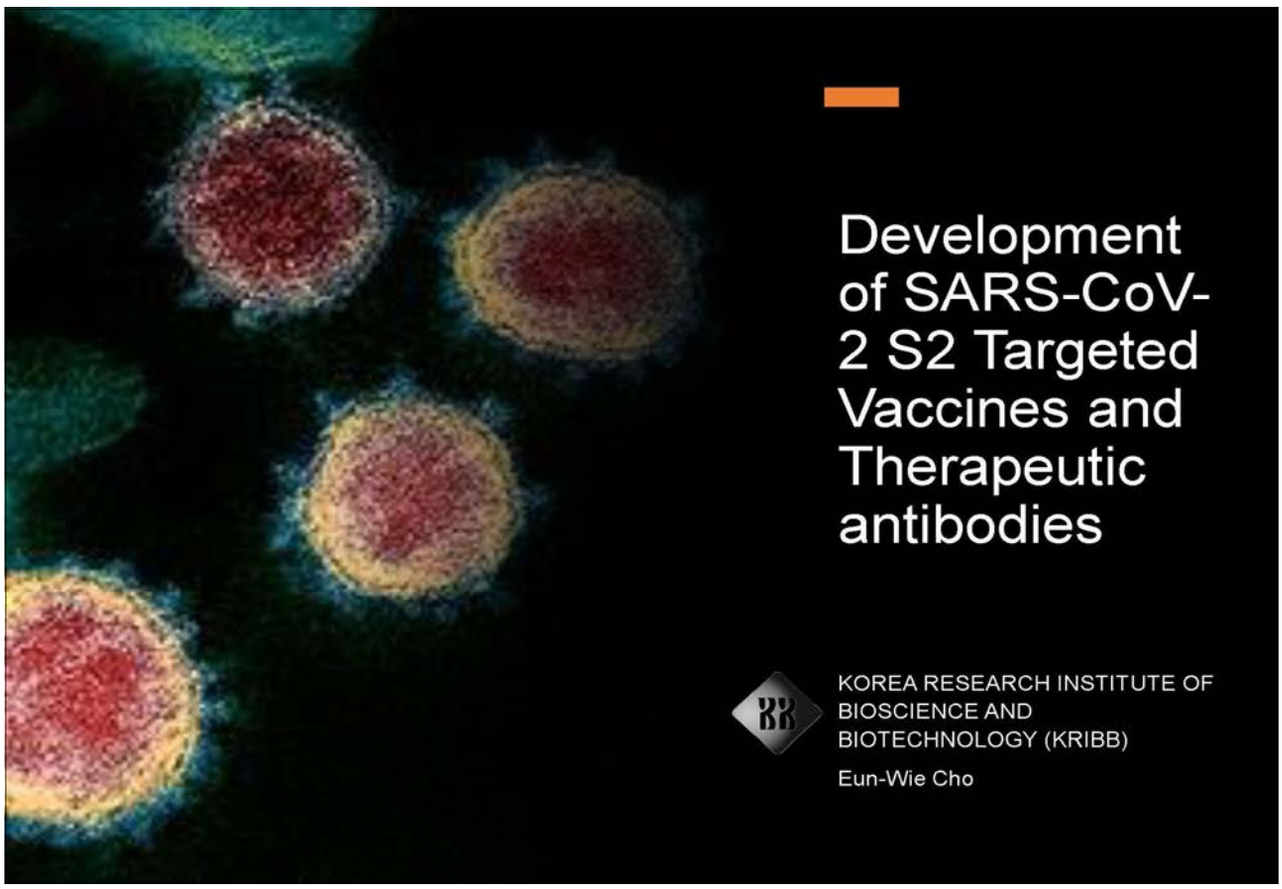
- 2007~Present Principal Researcher, Rare Disease Research Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB)
- 2010~2024 Adjunct professor, University of Science and Technology (UST)

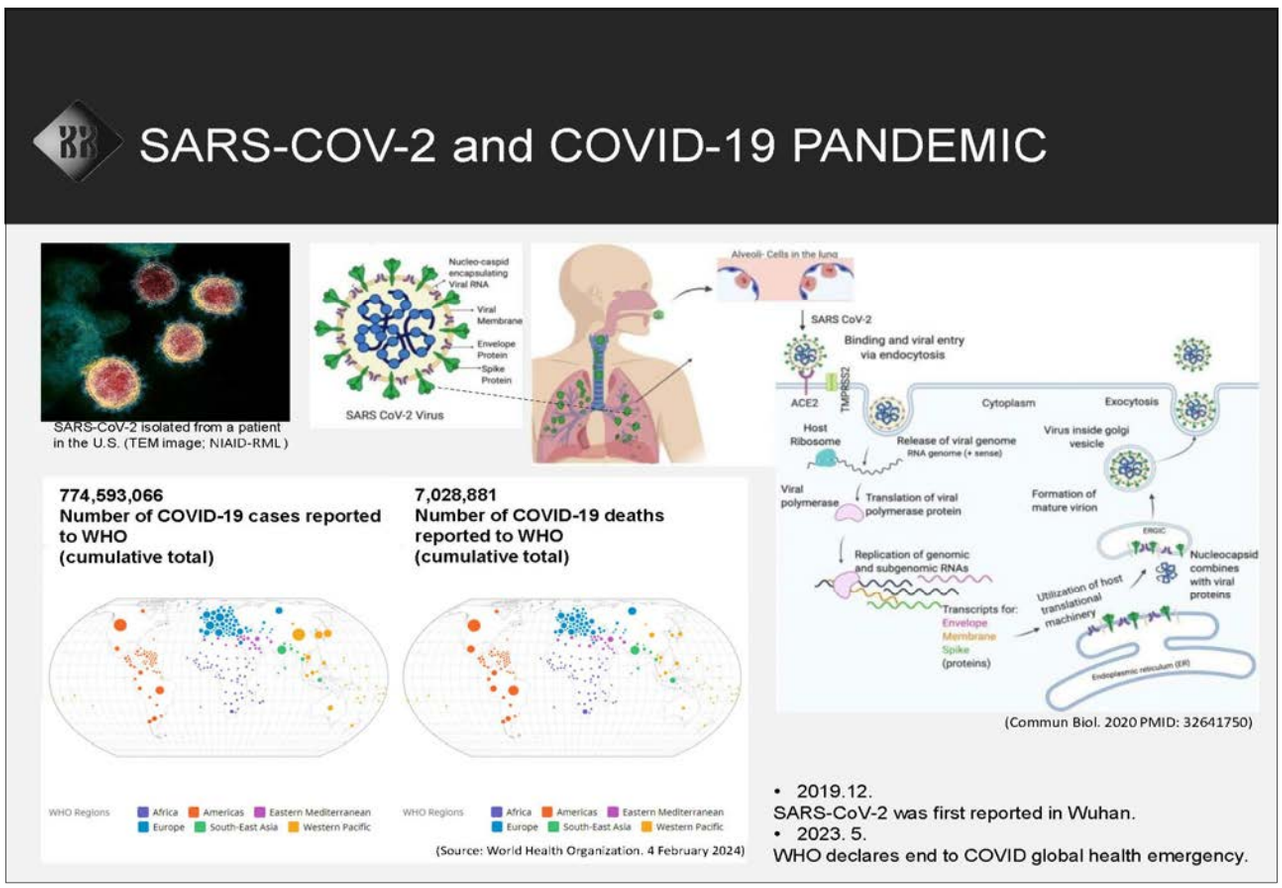
Topic

Development of SARS-CoV-2 S2 Targeted Vaccines and Therapeutic Antibodies

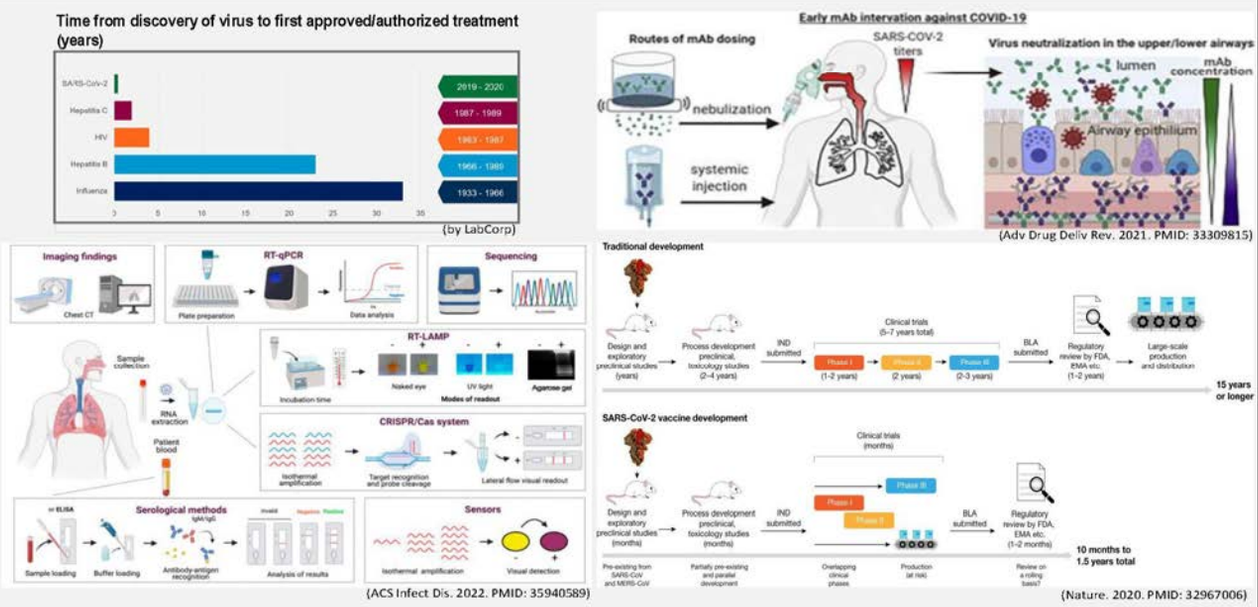
Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), had a major impact on both the global health and economy. Numerous virus-neutralizing antibodies were developed against the S1 subunit of SARS-CoV-2 spike (S) protein to block viral binding to host cells and were authorized for control of the COVID-19 pandemic. However, frequent mutations in the S1 subunit of SARS-CoV-2 enabled the emergence of immune evasive variants. To address these challenges, broadly neutralizing antibodies targeting the relatively conserved S2 subunit and its epitopes have been investigated as antibody therapeutics and universal vaccines. In this talk, we will present our findings, focusing on the properties of S2 antibodies and progress in the development of S2 peptide vaccines. We expect that these findings will lead to the design of S2 vaccines with improved efficacy and the discovery of therapeutic antibodies with high potency.

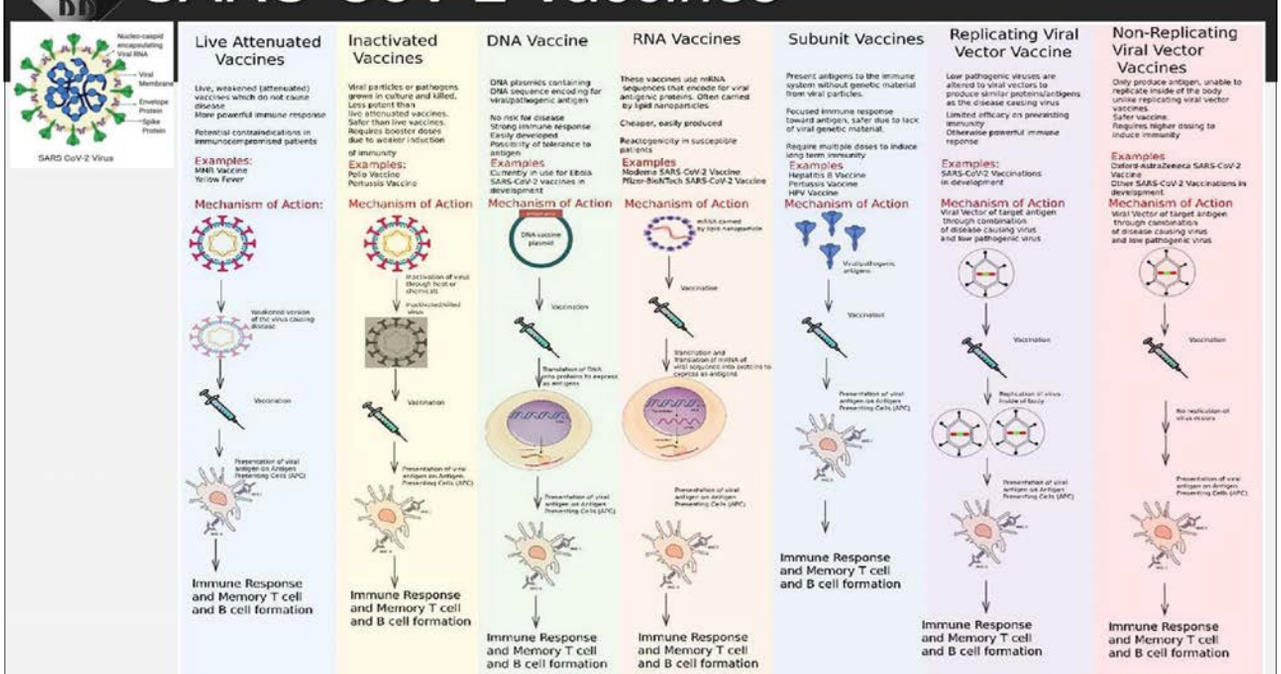

Development of SARS-CoV-2 S2 Targeted Vaccines and Therapeutic antibodies
KOREA RESEARCH INSTITUTE OF BIOSCIENCE AND BIOTECHNOLOGY (KRIBB)
Eun-Wie Cho


SARS-COV-2 and COVID-19 PANDEMIC
SARS-CoV-2 isolated from a patient in the U.S. (TEM image; NIAID-RML)
Nucleo-caspid encapsulating Viral RNA
Viral Membrane
Envelope Protein
Spike Protein
SARS CoV-2 Virus
Alveoli- Cells in the lung
SARS CoV-2
Binding and viral entry via endocytosis
ACE2
TMPRSS2
Cytoplasm
Exocytosis
Host Ribosome
Release of viral genome
RNA genome (+ sense)
Virus inside golgi vesicle
Viral polymerase
Translation of viral polymerase protein
Formation of mature virion
ERGIC
Replication of genomic and subgenomic RNAs
Nucleocapsid combines with viral proteins
Utilization of host translational machinery
Transcripts for:
Envelope
Membrane
Spike
(proteins)
Endoplasmic reticulum (ER)
(Commun Biol. 2020 PMID: 32641750)
774,593,066
Number of COVID-19 cases reported to WHO
(cumulative total)
7,028,881
Number of COVID-19 deaths reported to WHO
(cumulative total)
WHO Regions
Africa
Americas
Eastern Mediterranean
Europe
South-East Asia
Western Pacific
(Source: World Health Organization. 4 February 2024)
• 2019.12.
SARS-CoV-2 was first reported in Wuhan.
• 2023. 5.
WHO declares end to COVID global health emergency.

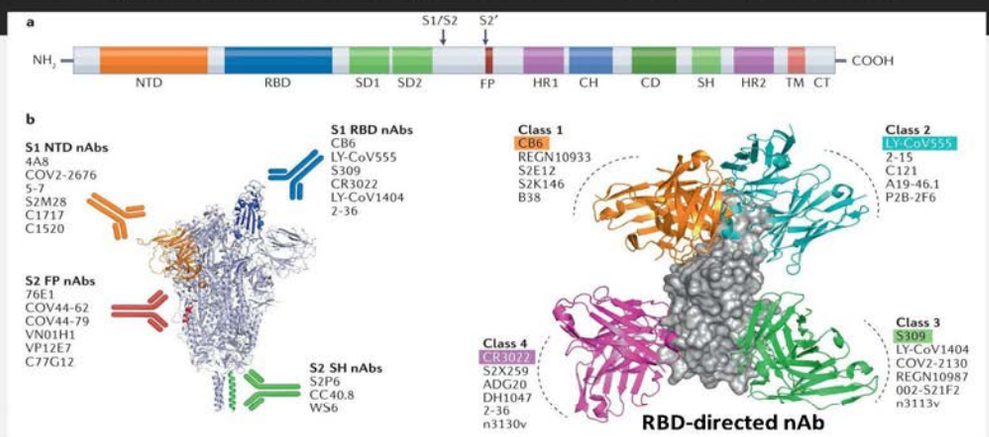
Responding to SARS-CoV-2:
Diagnostics, Vaccines and Therapeutic Antibodies



SARS-CoV-2 Vaccines



SARS-CoV-2 Therapeutic Antibodies:
Neutralizing antibodies directed against the SARS-CoV-2 spike protein



(Nat Rev Immunol. 2023. PMID: 36168054)

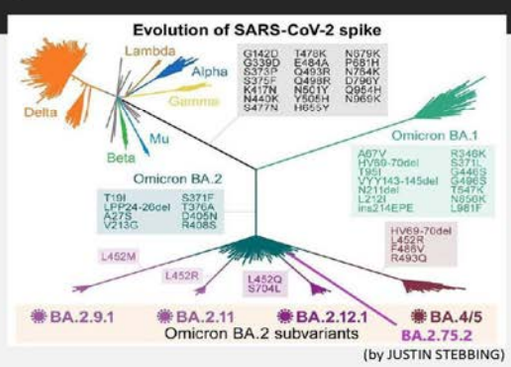
Table 1. FDA and/or EMA EUA therapeutic antibodies to treat COVID-19.

INN (a)	Other Names	Commercial Name	Company	EUA	
				FDA	EMA
Casirivimab	REGN 10933	REGEN-COV, Ronapreve	Regeneron Pharmaceuticals	21 November 2020 [9,10]	11 November 2021 [11,12]
Imdevimab	REGN 10987				
Bamlanivimab	BAM, LY3819253, LY-CoV555	N/A (b)	Eli Lilly and Company	9 February 2021 [13]	EMA withdrew the application on 29 October 2021 [14]
Etesevimab	CB6, ETE, LY3832479, LY-CoV016				
Sotrovimab	S309, VIR-7831 GSK 4182136	Xevudy	GlaxoSmithKline (GSK)	26 May 2021 [15]	16 December 2021 [16]
Regdanvimab	CT-P59	Regkirona	Celltrion	N/A	11 November 2021 [12,17]
Cilgavimab	COV2-2130, AZD1061	Evusheld	Astra Zeneca	8 December 2021 [18]	24 March 2022 [19]
Tixagevimab	COV2-2196, AZD8895				
Bebtelovimab	LY-CoV1404	N/A	Eli Lilly and Company	11 February 2022 [20]	N/A

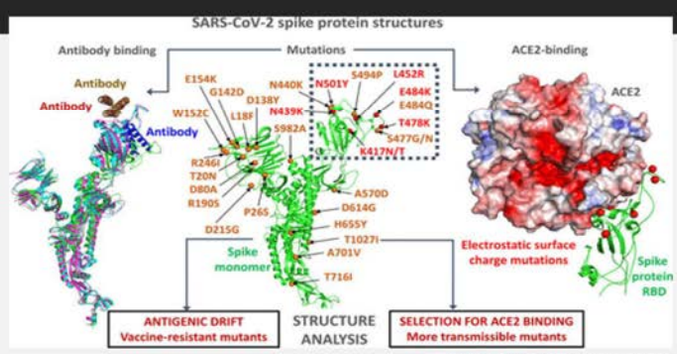
(a)—International proprietary name. (b)—N/A, non-applicable.

(Int J Mol Sci. 2022. PMID: 36077159)

Immune Evasion of SARS-CoV-2:
Evolution and Mutations of the SARS-CoV-2 Spike Protein

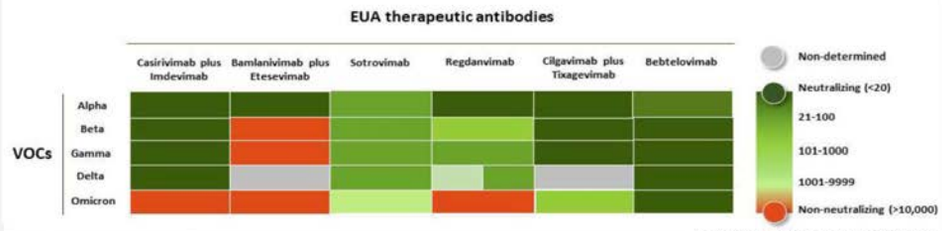


(by JUSTIN STEBBING)



(ACS Infect. Dis. 2022, 8, 1, 29-58)

Neutralization potency of the EUA-approved anti-COVID-19 antibodies when challenged with SARS-CoV-2 VOCs.
(The heat-map based on the neutralization values of pseudovirus assays against SARS-CoV-2 variants)



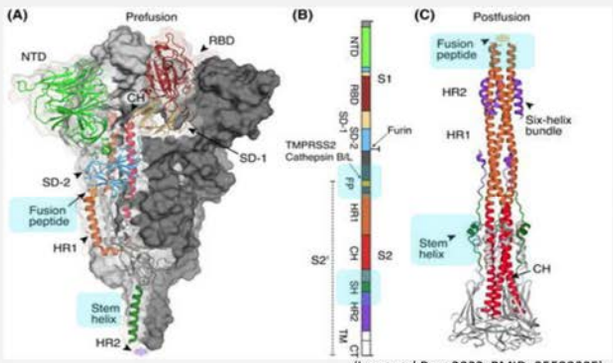
(Int J Mol Sci. 2022. PMID: 36077159)

2022

Broadly neutralizing antibodies to SARS-CoV-2 and other human coronaviruses

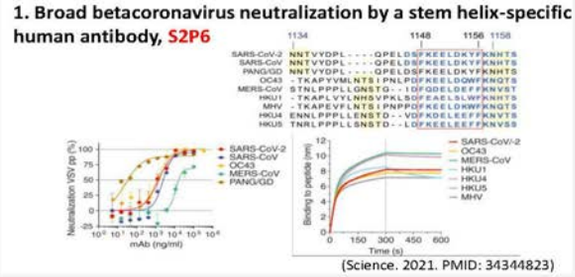
Broadly neutralizing epitopes in S2 subunit

1. S2 stem helix
2. Fusion peptide



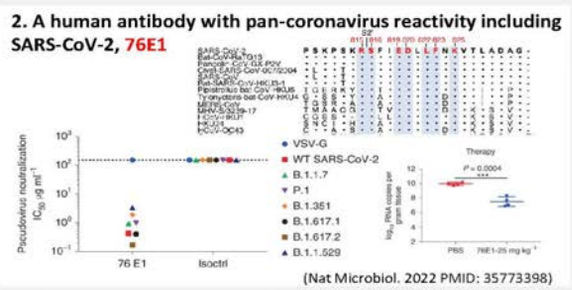
(Immunol Rev. 2022. PMID: 35599305)

1. Broad betacoronavirus neutralization by a stem helix-specific human antibody, S2P6



(Science. 2021. PMID: 34344823)

2. A human antibody with pan-coronavirus reactivity including SARS-CoV-2, 76E1



(Nat Microbiol. 2022 PMID: 35773398)

✓ *incredibly broad neutralization spectrum against HCoVs (α-CoVs, β-CoVs)*
✓ *less potent than RBD-targeting antibodies.*

2022

Broadly neutralizing antibodies to SARS-CoV-2 and other human coronaviruses

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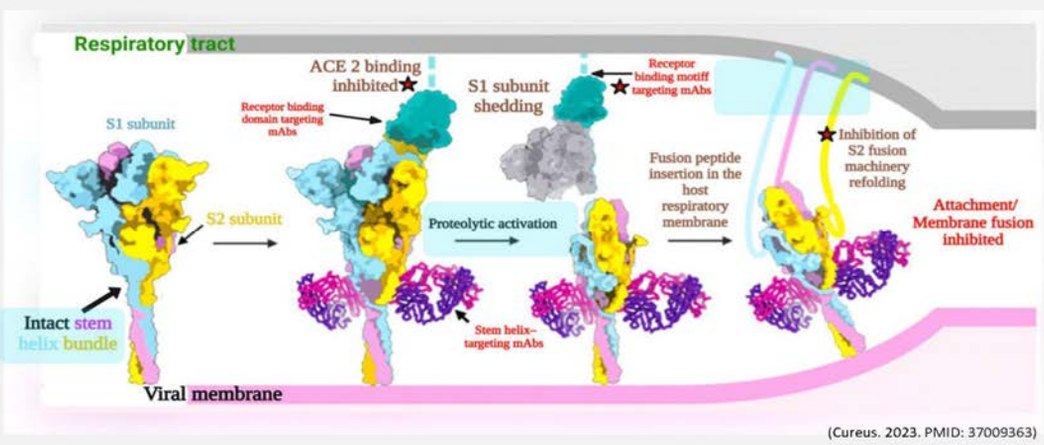
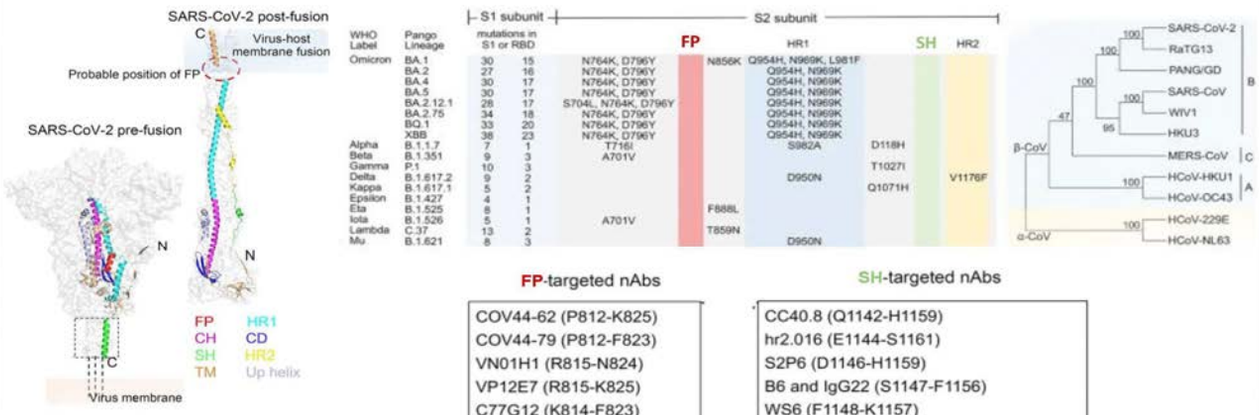


(Cureus. 2023. PMID: 37009363)

✓ *incredibly broad neutralization spectrum against HCoVs (α-CoVs, β-CoVs)*
✓ *less potent than RBD-targeting antibodies.*

Universal Vaccine Design to SARS-CoV-2 and other human coronaviruses

- S2 targeted universal vaccine
- Immuno-focusing on broadly neutralizing epitopes



FP-targeted nAbs

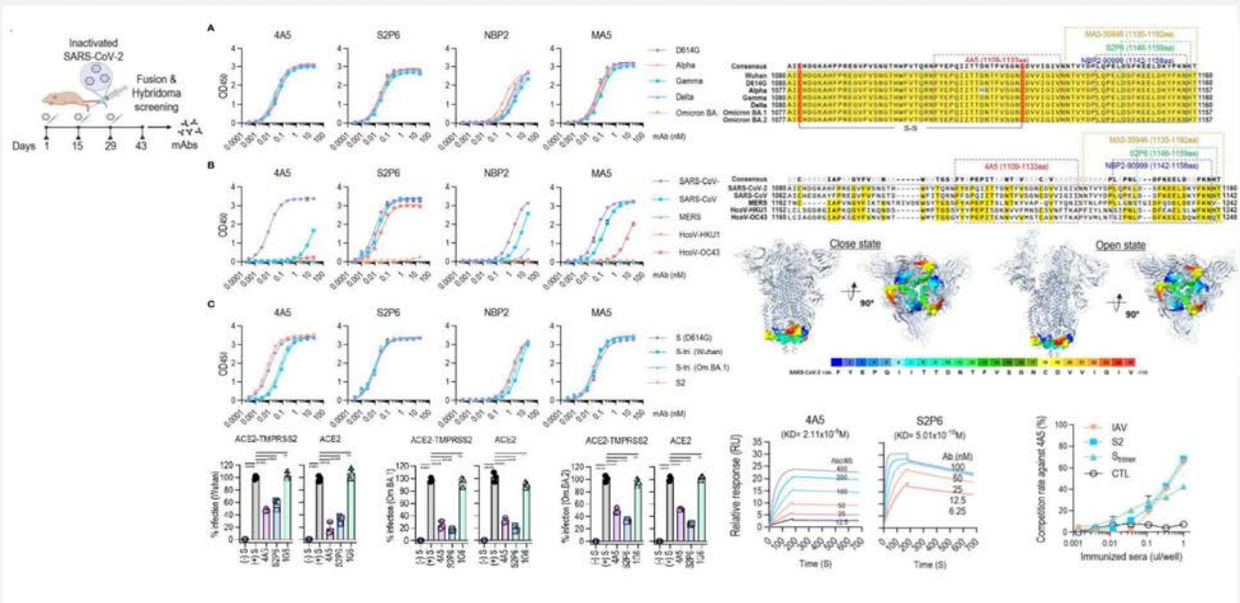
COV44-62 (P812-K825)
COV44-79 (P812-F823)
VN01H1 (R815-N824)
VP12E7 (R815-K825)
C77G12 (K814-F823)
76E1 (R815-K825)
Fp.006 (S813-K825)

SH-targeted nAbs

CC40.8 (Q1142-H1159)
hr2.016 (E1144-S1161)
S2P6 (D1146-H1159)
B6 and IgG22 (S1147-F1156)
WS6 (F1148-K1157)
CC25.106, CC95.108, CC68.109,
CC99.103, and CC95.102 (F1148-N1158)
28D9 and 1.6C7 (E1150-K1157)
CV3-25 (D1153-L1166)

(Signal Transduct Target Ther. 2023. PMID: 37164987)

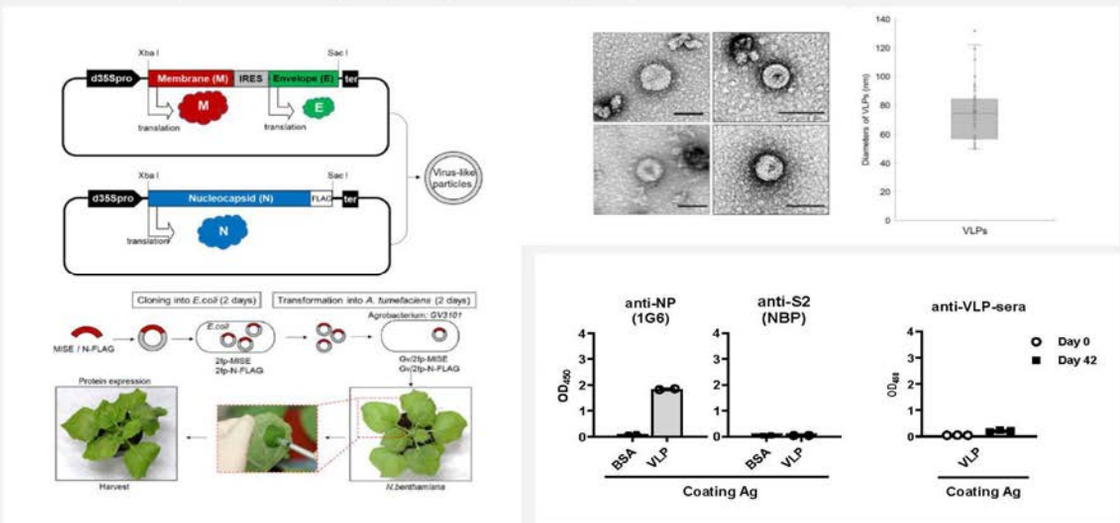
A Novel Broadly Neutralizing SARS-COV-2 S2 antibody, 4A5



(Heo CK et. al. Front Immunol. 2023 PMID: 38143750)

SARS-CoV-2 S2-based Universal Vaccine

- Focusing on immunodominant B cell epitopes in S2 subunit
- **Viral Nanoparticle displaying B cell epitopes**



(Moon KB et al. Sci Rep. 2022. PMID: 35046461)

(Unpublished Data)

SARS-CoV-2 S2-based Universal Vaccine

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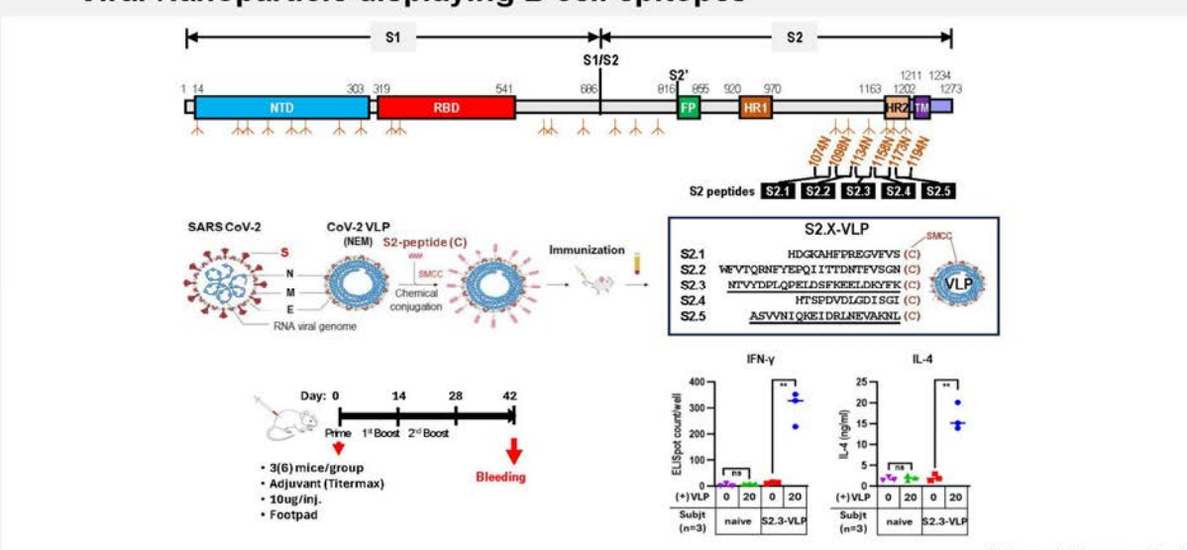
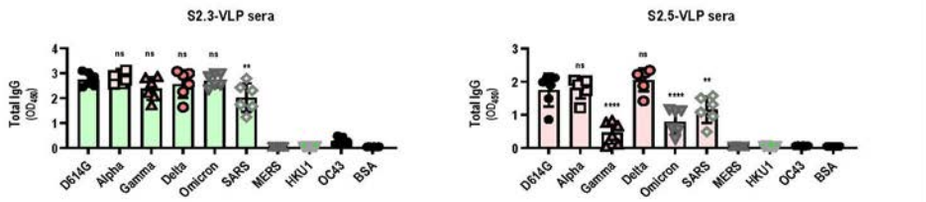


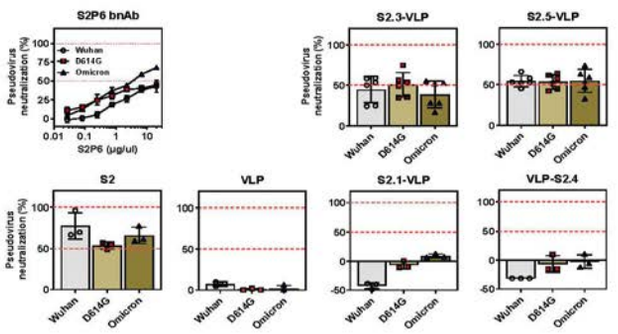
(Manuscript in preparation)

SARS-CoV-2 S2-based Universal Vaccine

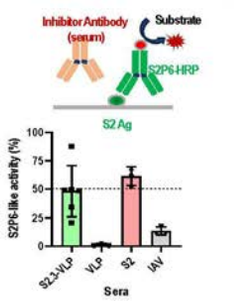
- **ELISA binding of mouse sera to S proteins of SARS-CoV-2 variants**



- **SARS-CoV-2 pseudovirus neutralization of mouse sera**



- **S2P6 bnAb-like activity**



(Manuscript in preparation)

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6. Broadly neutralizing antibodies to SARS-CoV-2 and other human coronaviruses. Chen Y, et al., Nat Rev Immunol. 2023. PMID: 36168054
7. Evolution of Anti-SARS-CoV-2 Therapeutic Antibodies. Almagro JC et. al. Int J Mol Sci. 2022. PMID: 36077159
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9. Evolution of Anti-SARS-CoV-2 Therapeutic Antibodies. Almagro JC et al., Int J Mol Sci. 2022. PMID: 36077159
10. Protective neutralizing epitopes in SARS-CoV-2. Liu H. et al., Immunol Rev. 2022. PMID: 35599305
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12. Neutralization mechanism of a human antibody with pan-coronavirus reactivity including SARS-CoV-2. Sun X et al., Nat Microbiol. 2022. PMID: 35773398
13. Exploring the Potential of Broadly Neutralizing Antibodies for Treating SARS-CoV-2 Variants of Global Concern in 2023: A Comprehensive Clinical Review. Gutlapalli SD et al., Cureus. 2023. PMID: 37009363
14. Targetable elements in SARS-CoV-2 S2 subunit for the design of pan-coronavirus fusion inhibitors and vaccines. Guo L et al., Signal Transduct Target Ther. 2023. PMID: 37164987
15. Novel S2 subunit-specific antibody with broad neutralizing activity against SARS-CoV-2 variants of concern. Heo CK et al., Front Immunol. 2023. PMID: 38143750
16. Construction of SARS-CoV-2 virus-like particles in plant. Moon KB et al., Sci Rep. 2022. PMID: 35046461
17. S2-peptide conjugated SARS-CoV-2 VLPs elicit broad protection against SARS-CoV-2 variants of concern. Heo CK et al., Manuscript in preparation

Research team members

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Jihyun Yang, Doo-Jin Kim
(Infectious Disease Research Center, KRIBB)
Ki-Beom Moon, Hyun-Soon Kim
(Plant Systems Engineering Research Center, KRIBB)
Sumin Son, Sang Jick Kim
(Synthetic Biology and Bioengineering Research Center, KRIBB)
Haryoung Poo
(Department of Biomedical Science and Engineering, Konkuk University)

Development of SARS-CoV-2 S2 Targeted Vaccines and Therapeutic antibodies


Development of SARS-CoV-2 S2 Targeted Vaccines and Therapeutic antibodies
THANK YOU FOR YOUR ATTENTION
KRIBB
CHO, Eun-Wie

03

코로나19로부터의 항바이러스제 개발 교훈

한수봉 센터장
한국화학연구원

Speaker

Soo Bong Han

- Korea Research Institute of Chemical Technology (KRICT)
- Principal Research Scientist/Head of Infectiou Diseases Therapeutic Research Centers

EDUCATION:

- 2010 The Univerity of Texas at Austin, Ph.D. in Chemistry
- 2004 KAIST, Master of Science in Chemistry
- 2002 Sogang University, Bachelor of Science in Chemistry

PROFESSIONAL EXPERIENCE:

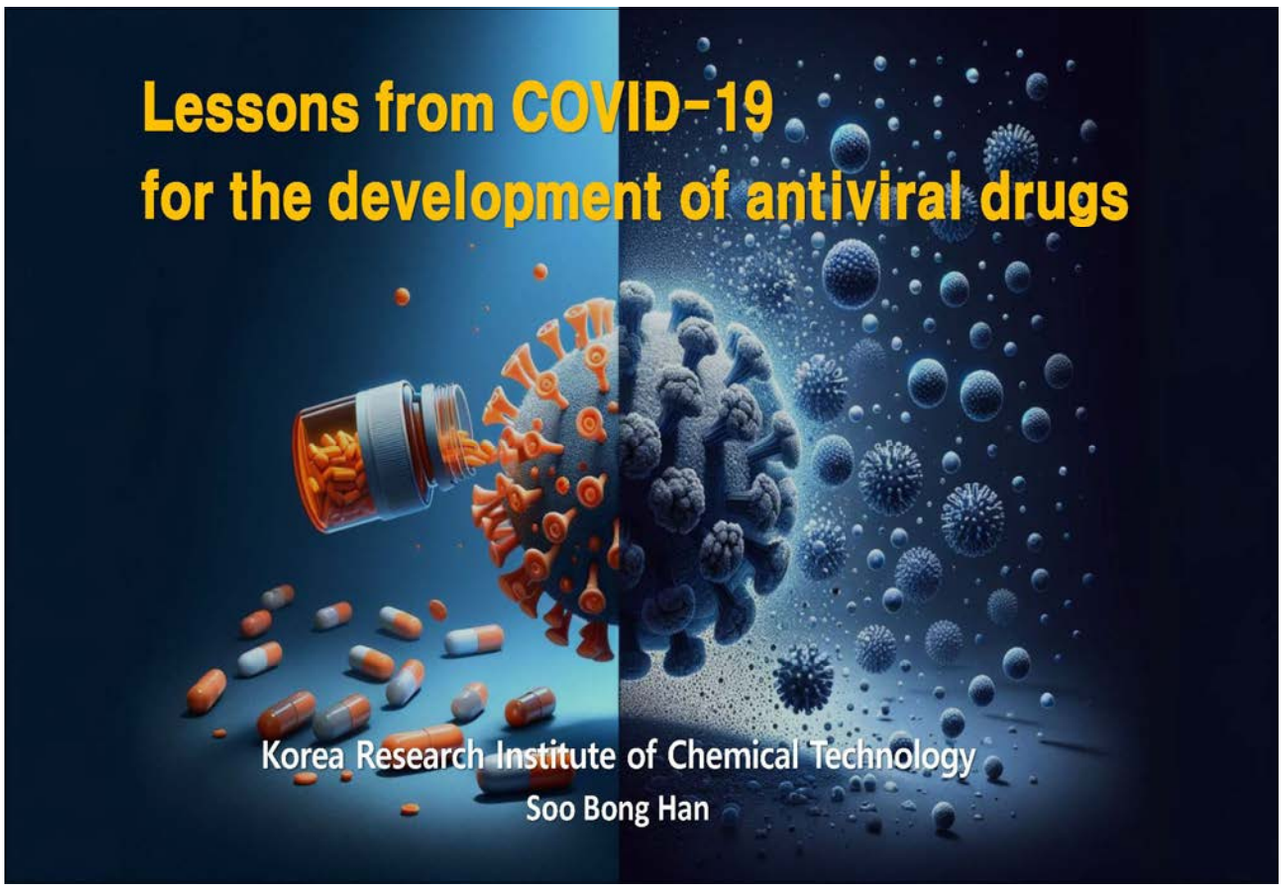
- 2023 ~ Present Head of Infectious Disease Therapeutics Research Center, KRICT
- 2018 ~ 현재 Principal Research Scientist, KRICT
- 2020 ~ 2022 Director of Department of Infectious Disease Research, KRICT
- 2018 ~ 2020 Head of Innovative Therapeutic Research Center
- 2012 ~ 2017 Senior Research Scientist, KRICT
- 2010 ~ 2011 Post-Doctoral Research Scientist, Princeton Univeristy

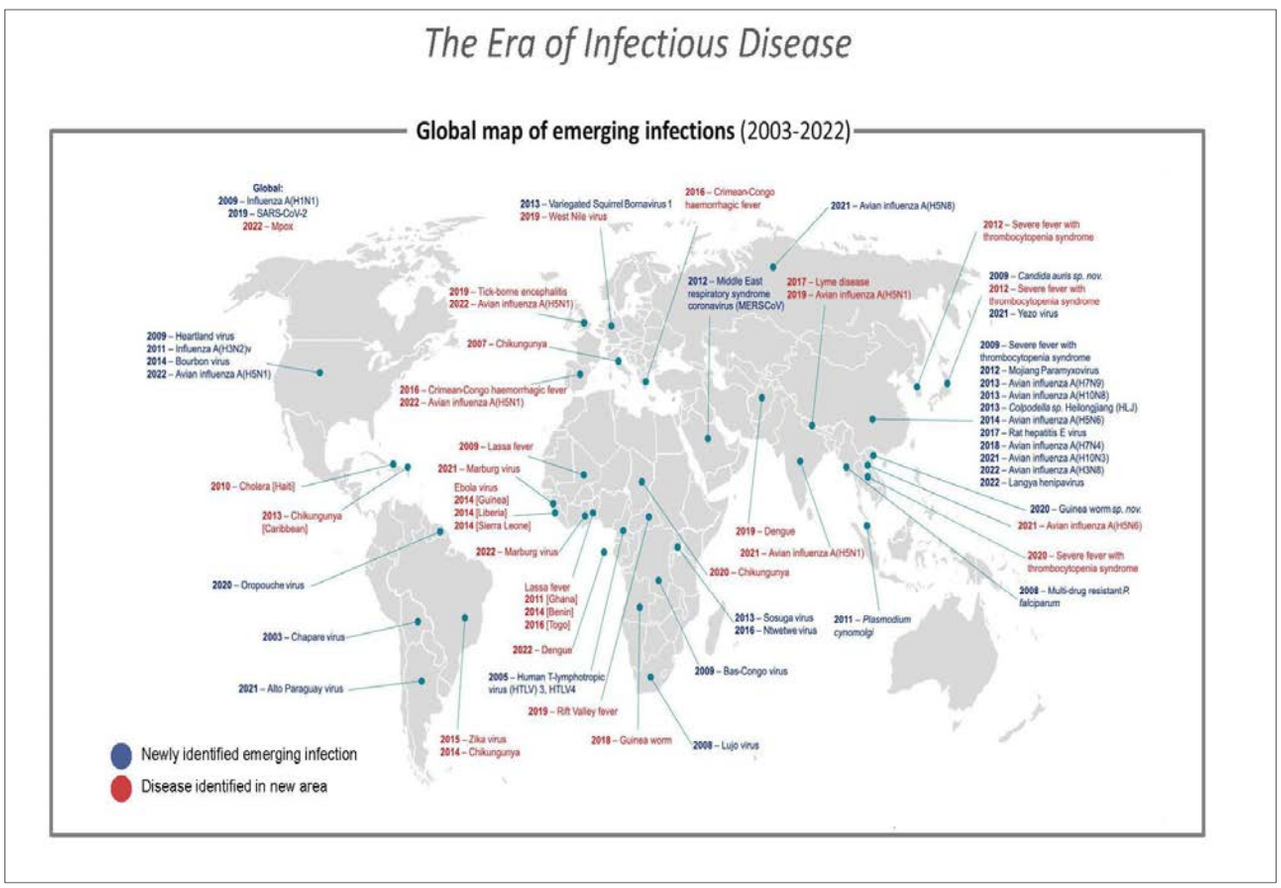
Topic

Lessons from COVID-19 for the development of antiviral drugs

Abstract

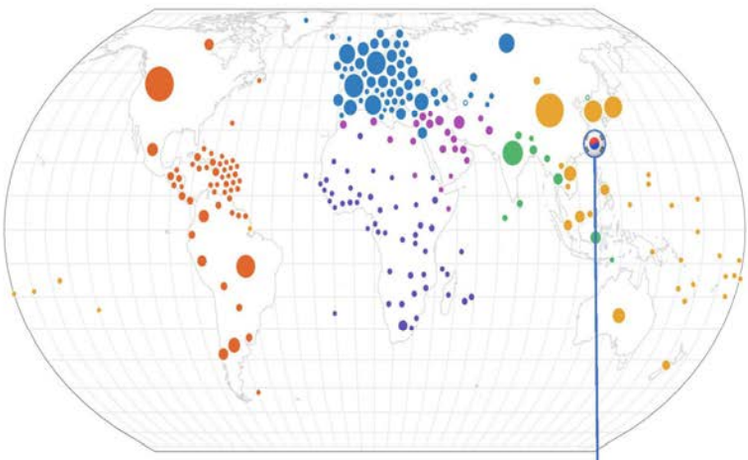
The global response to the COVID-19 pandemic has yielded significant insights that can guide the future development of antiviral drugs. It is important to address the valuable insights gained from the pandemic, which can be utilized to improve the efficiency and effectiveness of strategies for developing antiviral drugs. The urgency of the pandemic underscored the importance of expediting drug development without compromising safety, leveraging innovative technologies and collaborative approaches. Global cooperation and data sharing were paramount, highlighting the need for open communication and resource pooling. The value of broad-spectrum antiviral activity was underscored, offering a versatile approach to combatting multiple viral threats. Repurposing existing drugs for new indications proved successful, demonstrating the potential for accelerated responses. Given the rapid mutation rates of viruses, designing drugs to target critical points in viral replication cycles and considering adaptable drug designs are critical. Combination therapies emerged as a robust strategy, minimizing drug resistance and enhancing efficacy. Clinical trial readiness, sustained research investment, and equitable manufacturing and distribution strategies are essential to streamline drug development and ensure timely global access. In conclusion, the lessons derived from the COVID-19 pandemic offer a roadmap for optimizing antiviral drug development processes, ultimately bolstering global preparedness against future viral outbreaks.


Lessons from COVID-19
for the development of antiviral drugs
Korea Research Institute of Chemical Technology
Soo Bong Han


The Era of Infectious Disease
Global map of emerging infections (2003-2022)
Global:
2009 – Influenza A(H1N1)
2019 – SARS-CoV-2
2022 – Mpox
2013 – Variegated Squirrel Bornavirus 1
2019 – West Nile virus
2016 – Crimean-Congo haemorrhagic fever
2021 – Avian influenza A(H5N8)
2012 – Severe fever with thrombocytopenia syndrome
2012 – Middle East respiratory syndrome coronavirus (MERSCoV)
2017 – Lyme disease
2019 – Avian influenza A(H5N1)
2009 – Candida auris sp. nov.
2012 – Severe fever with thrombocytopenia syndrome
2021 – Yezo virus
2019 – Tick-borne encephalitis
2022 – Avian influenza A(H5N1)
2009 – Heartland virus
2011 – Influenza A(H3N2)v
2014 – Bourbon virus
2022 – Avian influenza A(H5N1)
2007 – Chikungunya
2016 – Crimean-Congo haemorrhagic fever
2022 – Avian influenza A(H5N1)
2009 – Severe fever with thrombocytopenia syndrome
2012 – Mojiang Paramyxovirus
2013 – Avian influenza A(H7N9)
2013 – Avian influenza A(H10N8)
2013 – Colpodella sp. Heilongjiang (HLJ)
2014 – Avian influenza A(H5N6)
2017 – Rat hepatitis E virus
2018 – Avian influenza A(H7N4)
2021 – Avian influenza A(H10N3)
2022 – Avian influenza A(H3N8)
2022 – Langya henipavirus
2009 – Lassa fever
2021 – Marburg virus
2010 – Cholera [Haiti]
Ebola virus
2014 [Guinea]
2014 [Liberia]
2014 [Sierra Leone]
2013 – Chikungunya [Caribbean]
2022 – Marburg virus
2020 – Guinea worm sp. nov.
2021 – Avian influenza A(H5N6)
2019 – Dengue
2021 – Avian influenza A(H5N1)
2020 – Chikungunya
2020 – Severe fever with thrombocytopenia syndrome
2008 – Multi-drug resistant P. falciparum
2020 – Oropouche virus
Lassa fever
2011 [Ghana]
2014 [Benin]
2016 [Togo]
2013 – Sosuga virus
2016 – Ntwetwe virus
2011 – Plasmodium cynomolgi
2003 – Chapare virus
2022 – Dengue
2009 – Bas-Congo virus
2005 – Human T-lymphotropic virus (HTLV) 3, HTLV4
2021 – Alto Paraguay virus
2019 – Rift Valley fever
2015 – Zika virus
2014 – Chikungunya
2018 – Guinea worm
2008 – Lujo virus
Newly identified emerging infection
Disease identified in new area

The Era of Infectious Disease

- Climate Change
- Increase in population mobility
- Aging
- Lack of effective treatment



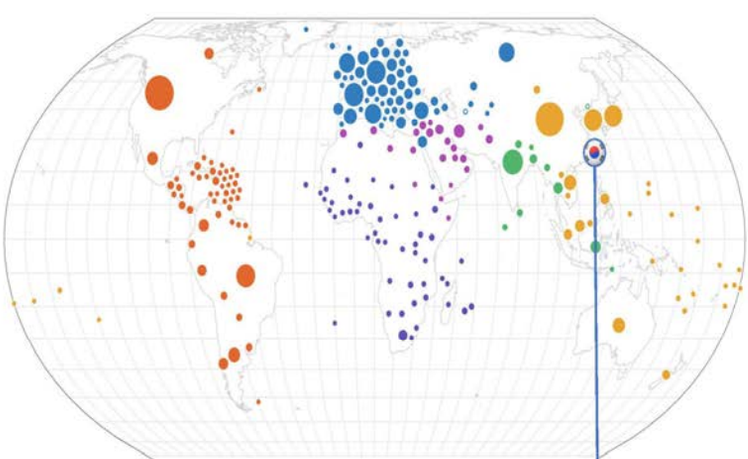
SARS-CoV-2

- **Confirmed cases**: 774,291,287
- **Death**: 7,019,704
- **Vaccine doses**: 13,516,282,548

34,571,873 (67%)
35,934
135,927,574 (263%)

COVID-19

Dignosis Vaccine Drug



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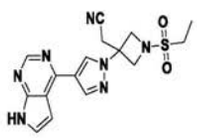
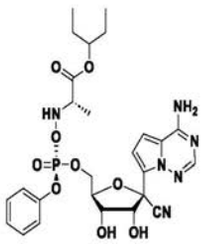
COVID-19

- **US-FDA approved Drug for COVID-19**

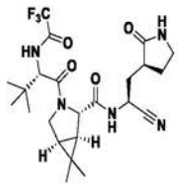


Baricitinib

Tocilizumab



Remdesivir



Nirmatrelvir

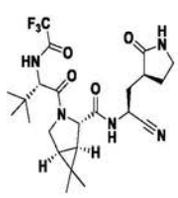
Rheumatoid Arthritis

Directing Acting Antiviral

*emergency use authorization not included

Paxlovid

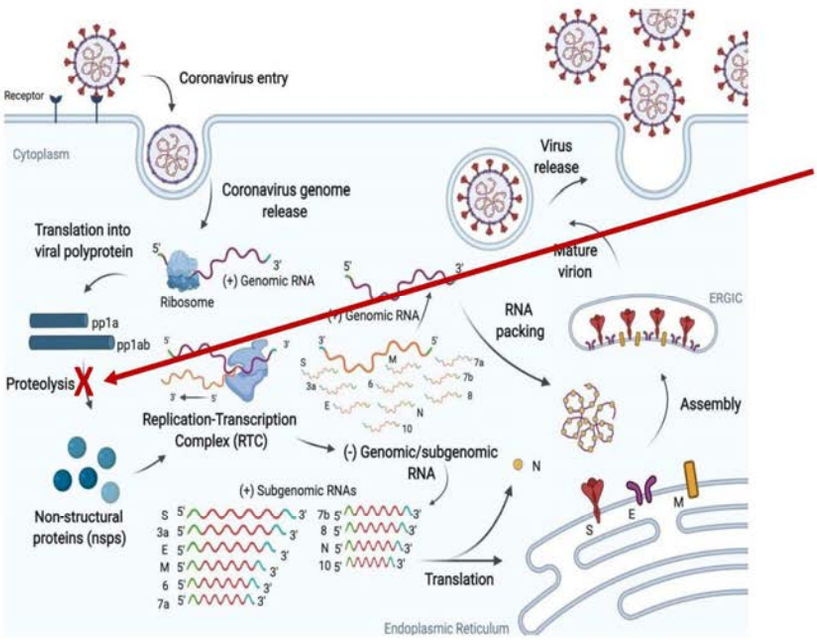
- **Top drugs by sales in 2022** (USD BD)



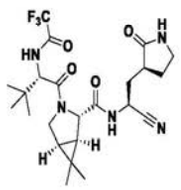
Nirmatrelvir

Paxlovid

- **Mode of Action : Direct-Acting Antiviral** (3CL protease inhibitor)



Virus life cycle (COVID-19)

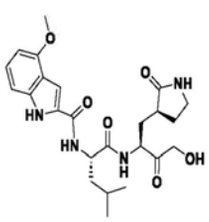


Nirmatrelvir

Paxlovid

KRICT 한국화학연구원

- **Existing Compound Optimization Strategy: 3CL protease inhibitor**



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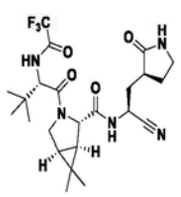

Nirmatrelvir

Science, **2021**, *374*, 1586

Paxlovid

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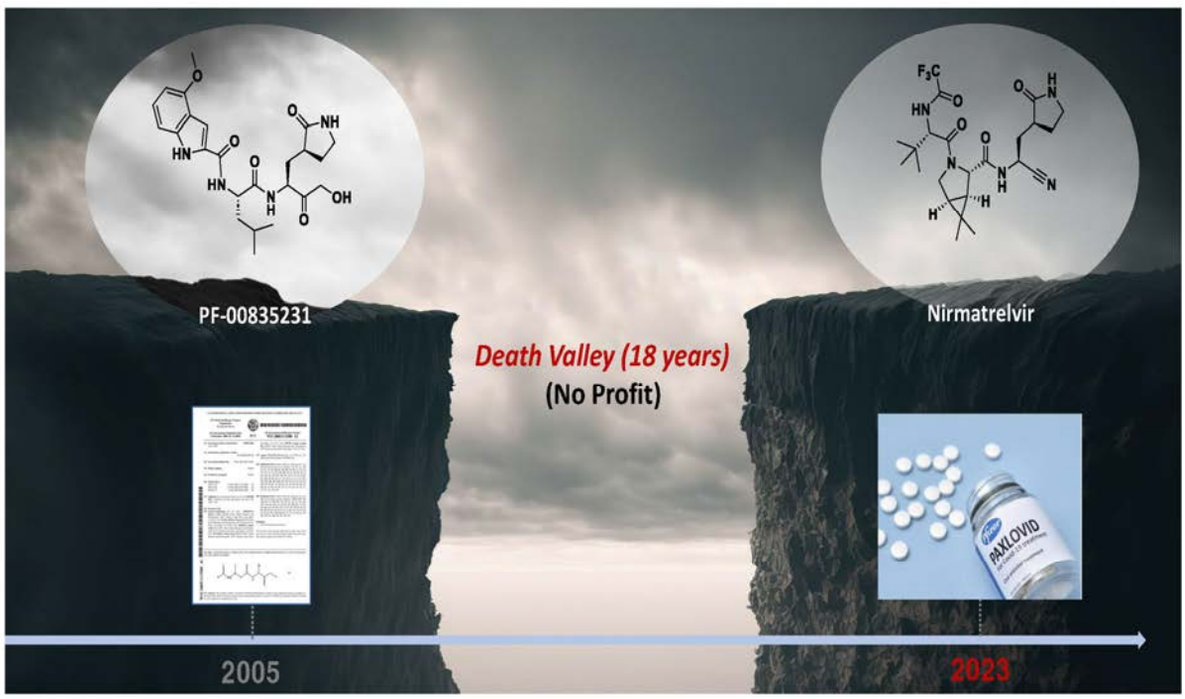
- Death Valley

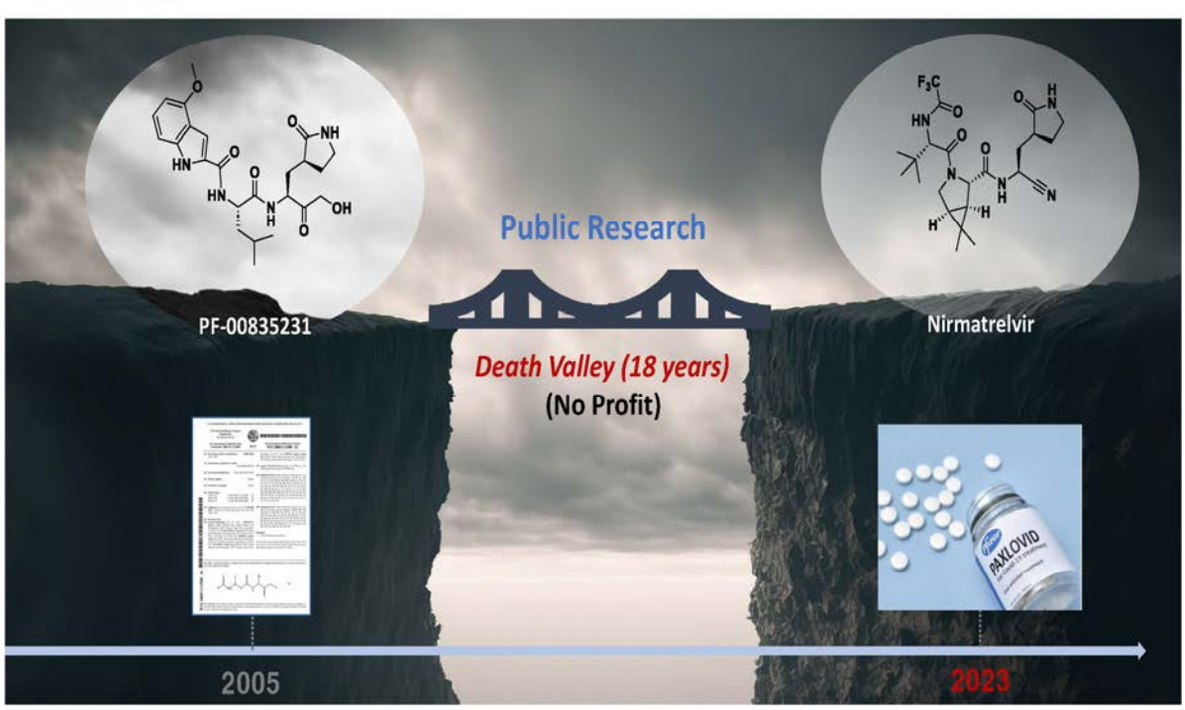


Science, **2021**, *374*, 1586

Paxlovid

KRICT 한국화학연구원

- Death Valley



Science, **2021**, *374*, 1586

KRICT Direct-Acting Antiviral Chemical Library

- **Existing Drugs and Compounds**

  Protease

  Polymerase

  Integrase

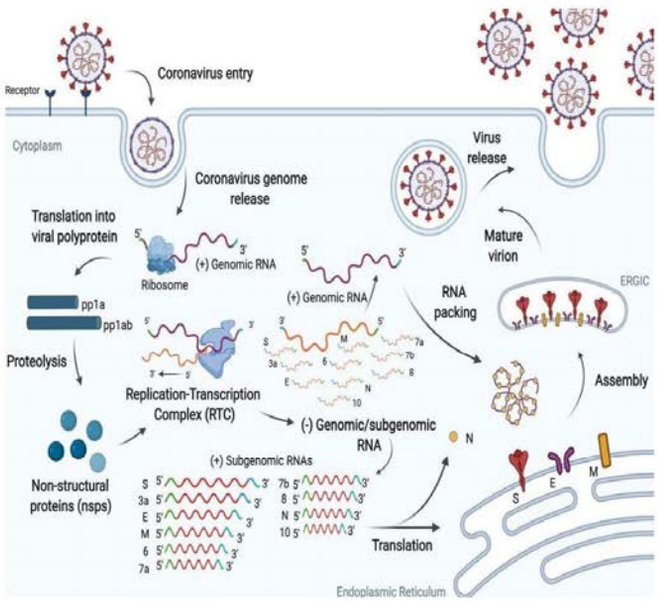
  Reverse transcriptase

  DNA/RNA synthetase

  Entry

  Etc.

Approved – Clinical – Biochemical



Virus life cycle (COVID-19)

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- **Goal - 1500 compounds** (500 compounds collected)

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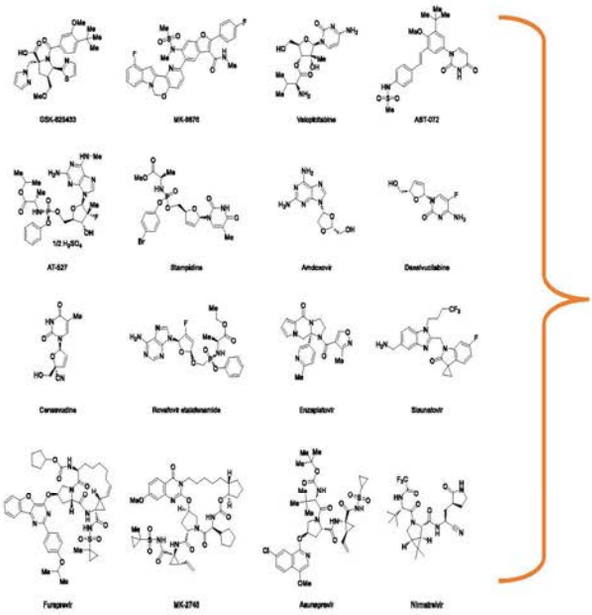
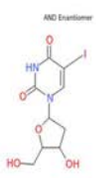


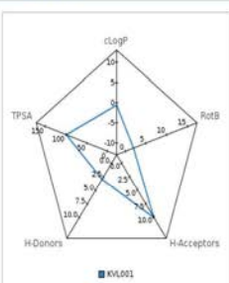
KRICT Direct-Acting Antiviral Chemical Library

- **Web-based DB platform for public use**

Infectous Disease Therapeutics DB

Display records 1 to 1 of 172 Update <<First <Previous Next> Last>>





KRICT Code	Product Name	Synonyms	CAS No	Purity
KVL001	Idoxuridine	'5-Iodo-2'-deoxyuridine	54-42-2	100

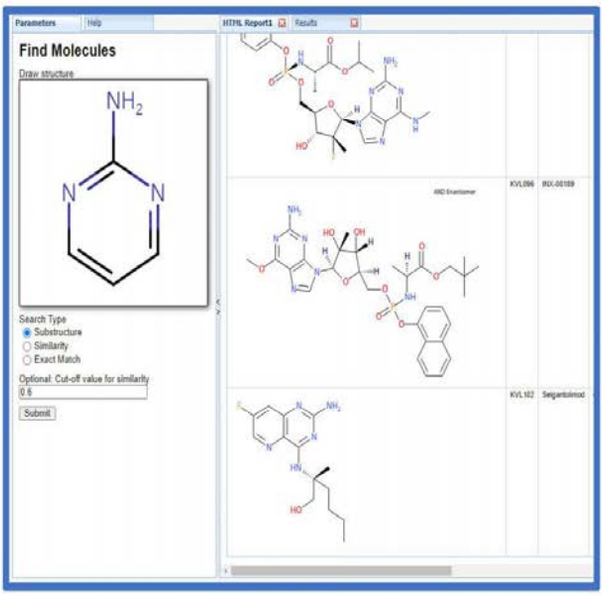
Clinical_Information	Pathway	Research_Area	Target	Class
Launched	Polymerase	Infection; Cancer	HSV	Polymerase1

Physicochemical properties

MW	HBA	HBD	cLogP	TPSA
354.09851	10	3	-0.53	99.10

KRICT Direct-Acting Antiviral Chemical Library

- **Web-based DB platform for public use**



KRICT Direct-Acting Antiviral Chemical Library

- **Advanced Antiviral Drug Library** (1000 compound)

AI based Chemical Library

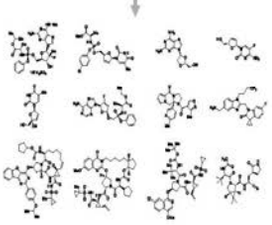
Antiviral Activity Data

ADME & Tox Data

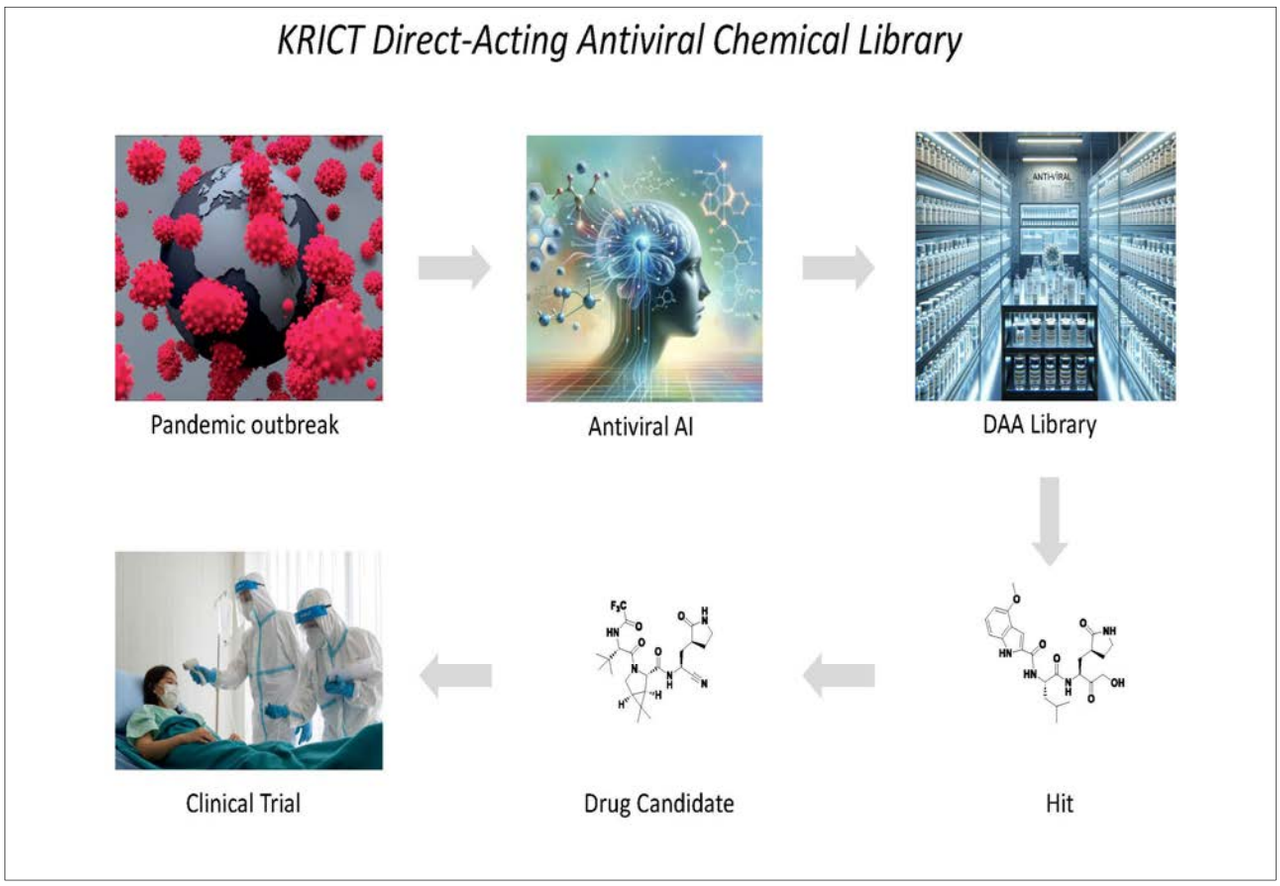
Antiviral Target Structure Data

Antiviral AI

Experiment



New Drug Structure Design


KRICT Direct-Acting Antiviral Chemical Library
Pandemic outbreak
Antiviral AI
DAA Library
Hit
Drug Candidate
Clinical Trial

04

인공지능 기반 신약개발 가속화

김우연 교수
한국과학기술원

Speaker

Woo-Youn Kim

- KAIST
- Professor, Department of Chemistry, KAIST

EDUCATION:

- 2009 Ph.D., Chemistry, POSTECH
- 2004 B.S., Chemistry & Physics, POSTECH

PROFESSIONAL EXPERIENCE:

- 2024 ~ Present Vice Director, Convergence AI Institute for Drug Discovery, Korea Pharmaceutical and Bio-Pharma Manufacturers Association
- 2022 ~ 2024 Director, Korea AI Center for Drug Discovery and Development, Korea Pharmaceutical and Bio-Pharma Manufacturers Association
- 2020 ~ Present Cofounder & CEO, HITS Inc.
- 2011 ~ Present Assist./Assoc./Full Professor, Chemistry, KAIST
- 2009 ~ 2010 Postdoctoral Fellow, Max-Planck-Institute

Topic

Acceleration of drug discovery with AI

Abstract

In recent years, deep learning-based AI has been rapidly developing, bringing significant impact on the field of drug discovery. For instance, AlphaFold has solved the problem of protein structure prediction and generative AI has been actively used for the design of proteins, antibodies, and small molecule drugs. Thus, leading IT companies such as Google DeepMind, MS, and Nvidia as well as big pharma such as AstraZeneca, Merck, and Pfizer are actively investing in the development of AI in this field. In this talk, I will briefly review the latest trends in AI-based drug discovery and introduce generative AI-based drug design research examples.

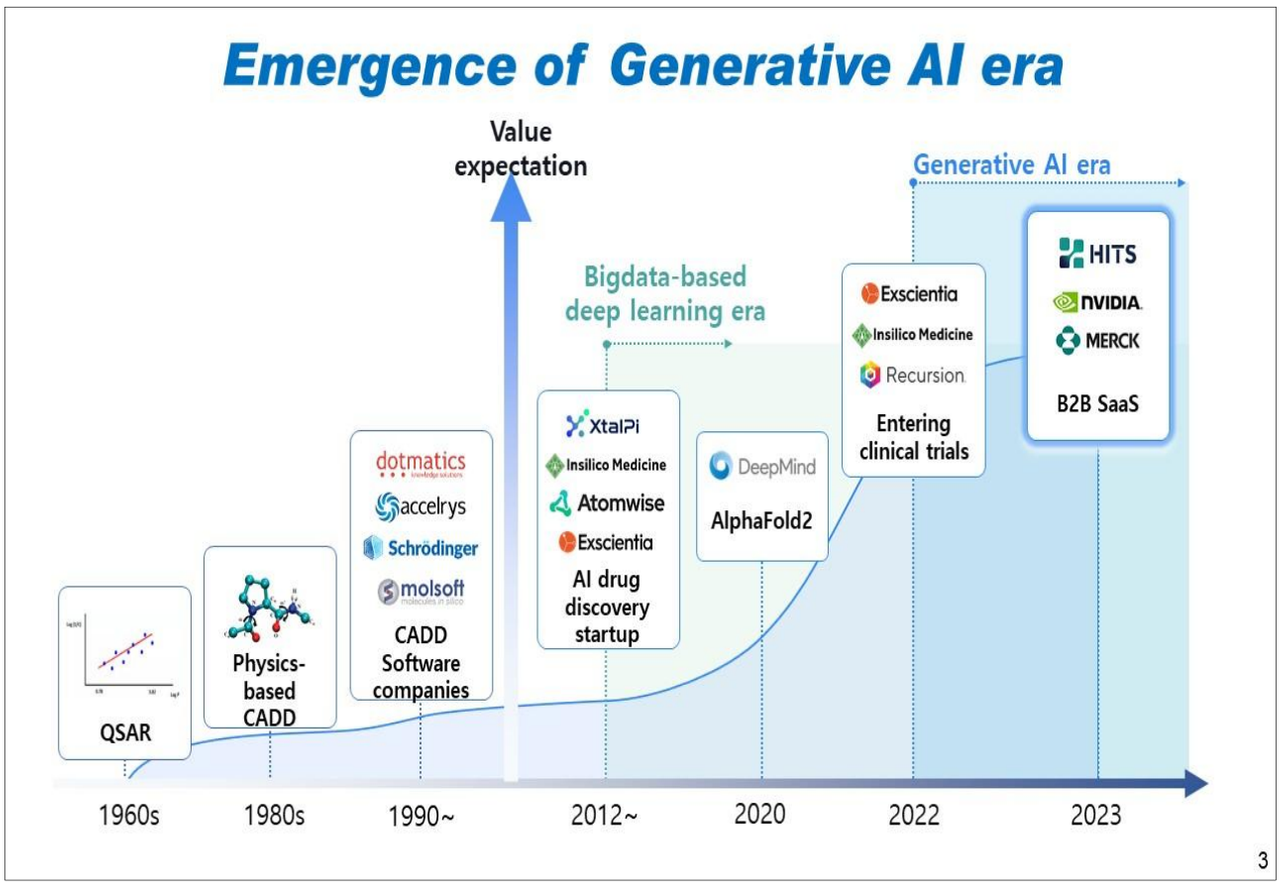
Acceleration of drug discovery with AI

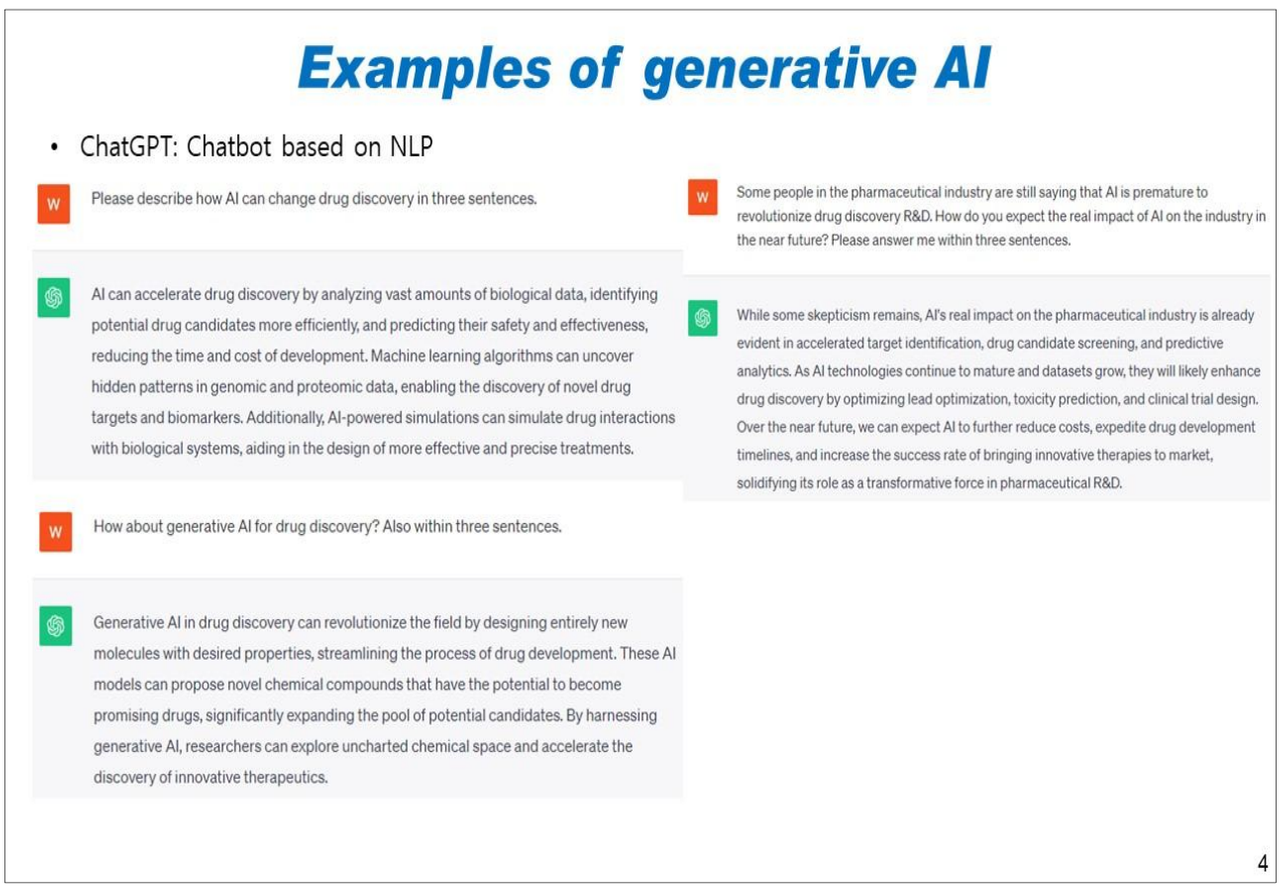
Woo Youn Kim
KAIST & HITS

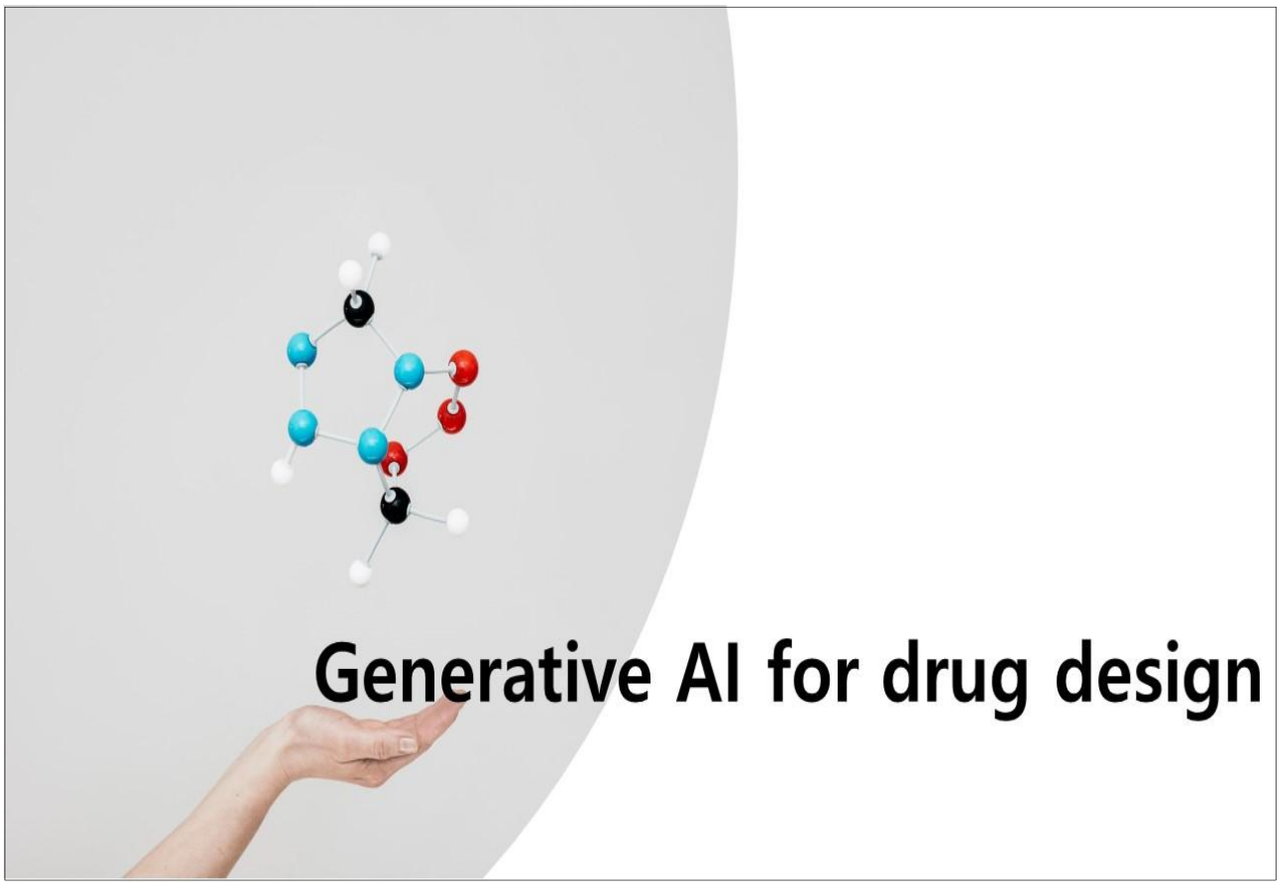
International Symposium for Infectious Diseases Research Institutes Cooperation
2024. 3. 8 @Grand Hyatt Incheon

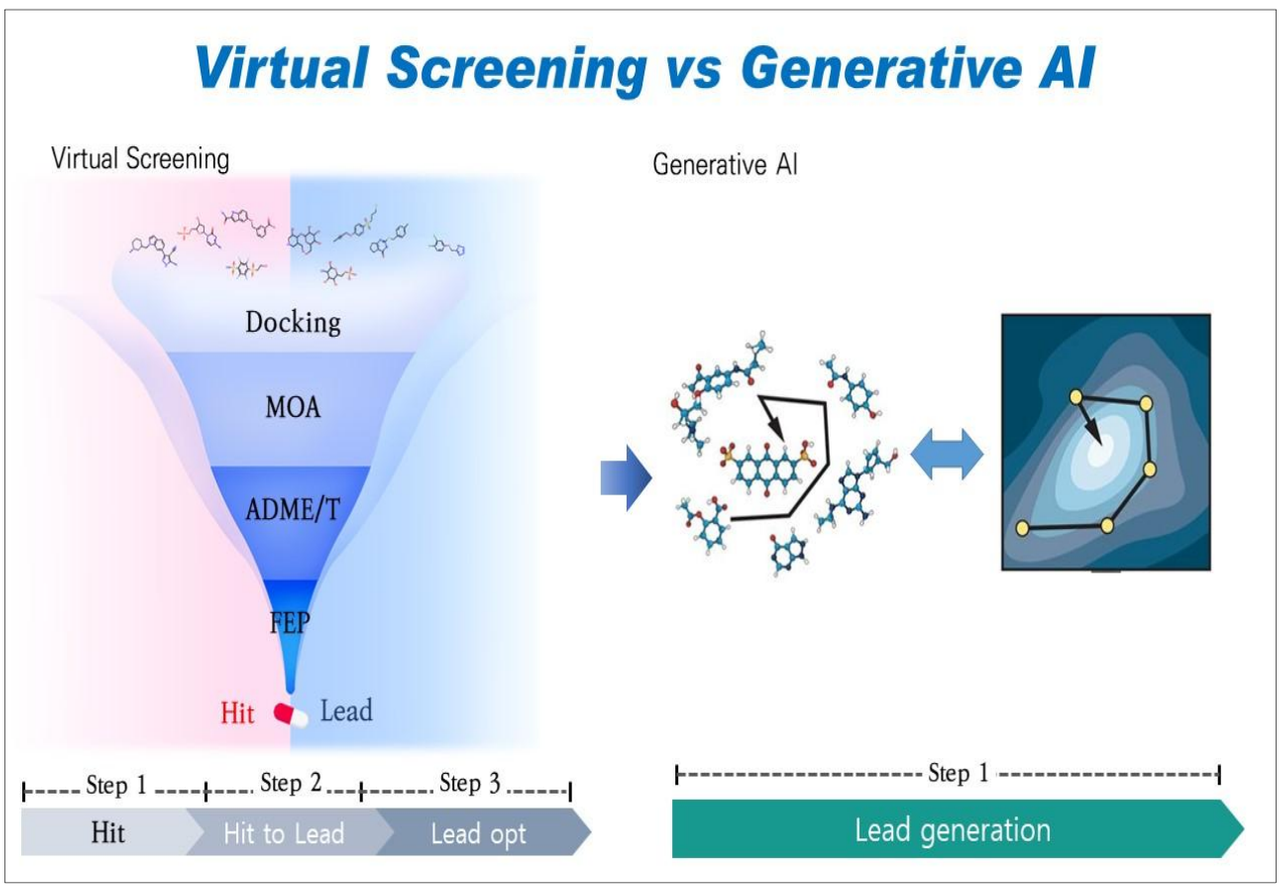
Contents

2

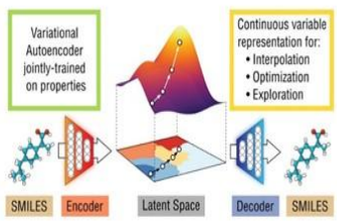

Emergence of Generative AI era
Value expectation
Generative AI era
Bigdata-based deep learning era
QSAR
Physics-based CADD
dotmatics
accelrys
Schrödinger
molsoft
CADD Software companies
XtalPi
Insilico Medicine
Atomwise
Exscientia
AI drug discovery startup
DeepMind
AlphaFold2
Exscientia
Insilico Medicine
Recursion
Entering clinical trials
HITS
NVIDIA
MERCK
B2B SaaS
1960s
1980s
1990~
2012~
2020
2022
2023
3


Examples of generative AI
• ChatGPT: Chatbot based on NLP
Please describe how AI can change drug discovery in three sentences.
AI can accelerate drug discovery by analyzing vast amounts of biological data, identifying potential drug candidates more efficiently, and predicting their safety and effectiveness, reducing the time and cost of development. Machine learning algorithms can uncover hidden patterns in genomic and proteomic data, enabling the discovery of novel drug targets and biomarkers. Additionally, AI-powered simulations can simulate drug interactions with biological systems, aiding in the design of more effective and precise treatments.
How about generative AI for drug discovery? Also within three sentences.
Generative AI in drug discovery can revolutionize the field by designing entirely new molecules with desired properties, streamlining the process of drug development. These AI models can propose novel chemical compounds that have the potential to become promising drugs, significantly expanding the pool of potential candidates. By harnessing generative AI, researchers can explore uncharted chemical space and accelerate the discovery of innovative therapeutics.
Some people in the pharmaceutical industry are still saying that AI is premature to revolutionize drug discovery R&D. How do you expect the real impact of AI on the industry in the near future? Please answer me within three sentences.
While some skepticism remains, AI's real impact on the pharmaceutical industry is already evident in accelerated target identification, drug candidate screening, and predictive analytics. As AI technologies continue to mature and datasets grow, they will likely enhance drug discovery by optimizing lead optimization, toxicity prediction, and clinical trial design. Over the near future, we can expect AI to further reduce costs, expedite drug development timelines, and increase the success rate of bringing innovative therapies to market, solidifying its role as a transformative force in pharmaceutical R&D.
4

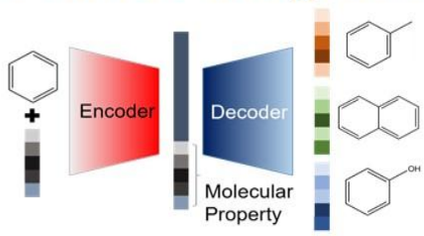

Generative AI for drug design


Virtual Screening vs Generative AI
Virtual Screening
Docking
MOA
ADME/T
FEP
Hit
Lead
Step 1
Step 2
Step 3
Hit
Hit to Lead
Lead opt
Generative AI
Step 1
Lead generation

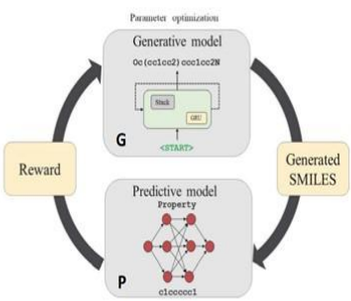
Early works in Generative AI for drug design



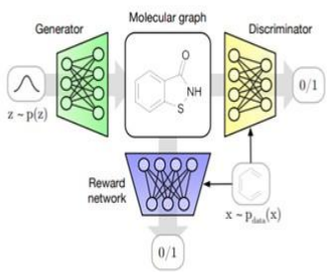
Variational autoencoder (**VAE**)
(ACS Cent. Sci. 2018, 4, 2, 268-276)



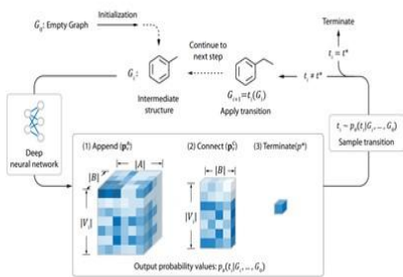
Conditional variational autoencoder (**CVAE**)
Lim et al., J. Cheminform. 10:31 (2018)



Reinforcement learning
(Science Advances, Vol. 4, no. 7, eaap7885)

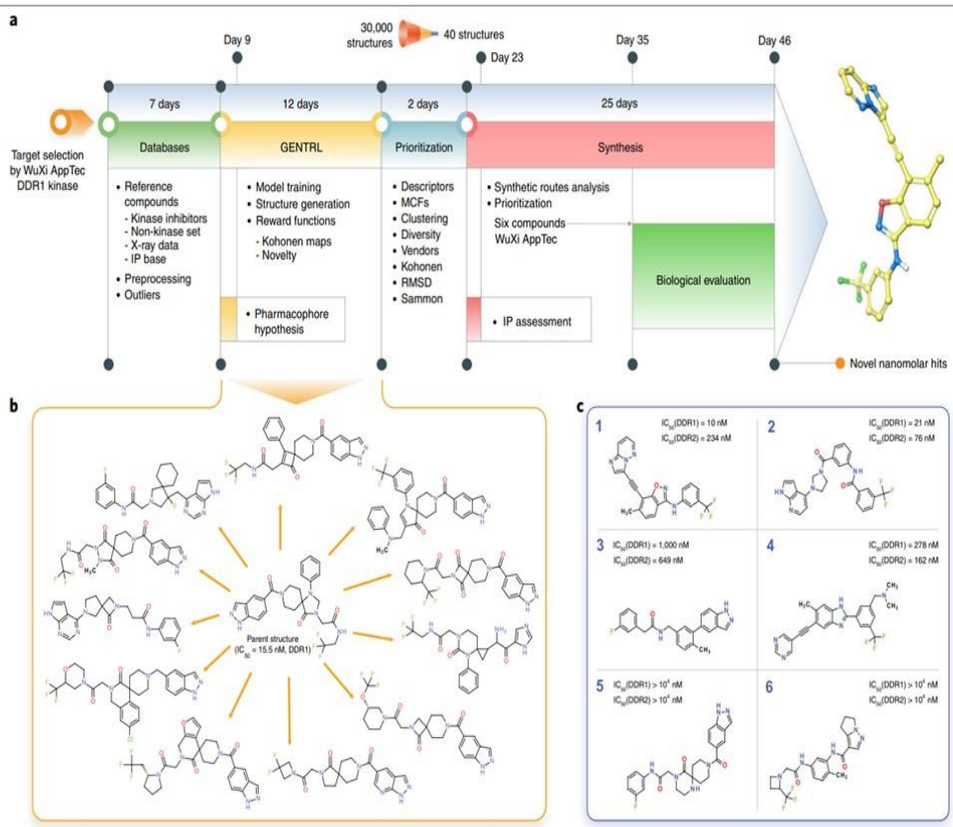


Generative adversarial network (**GAN**)
(Arxiv:1805.11973)



Graph generative model (**GAN**)
(Arxiv:1801.07299)

7



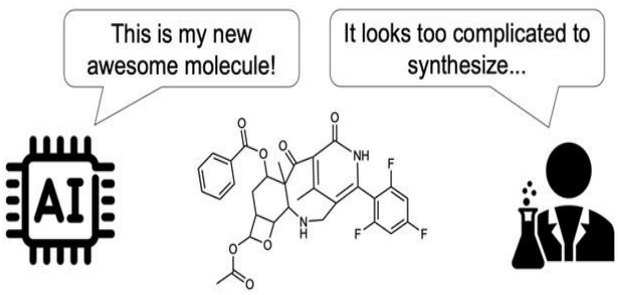
Nat. biotech. 37, 1038 (2019)

8

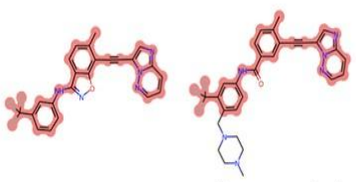
Generative AI for drug discovery

- Generative AI can efficiently explore a vast chemical space
- But conventional Gen AI has two key problems

1. Low synthesizability: atom-based or SMILES generation does not consider synthetic accessibility



2. Low novelty: overfitting to training data



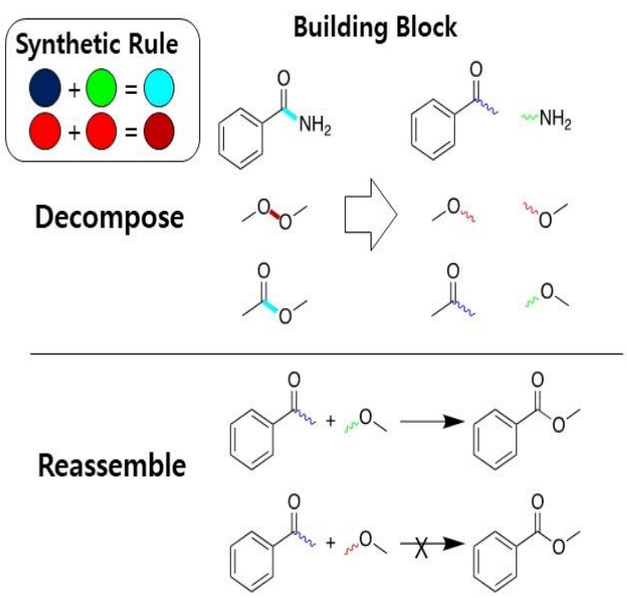
Designed by GENTRL Approved drug

Nat. biotech. 37, 1038 (2019)

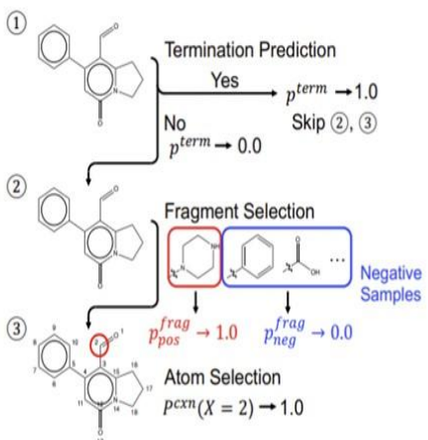
9

Improving synthesizability

Breaking **R**etrosynthetically **I**nteresting **C**hemical **S**ubstructures using BRICS decomposition



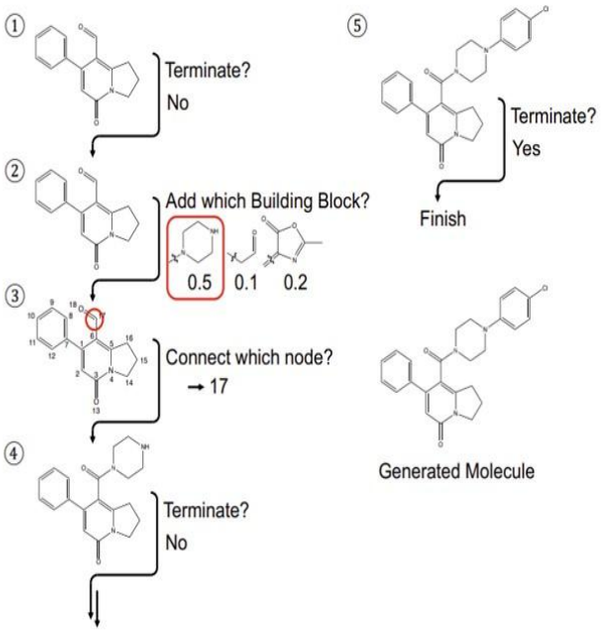
600,000 molecules chosen randomly from a chemical library, resulting in 70,000 unique building blocks.

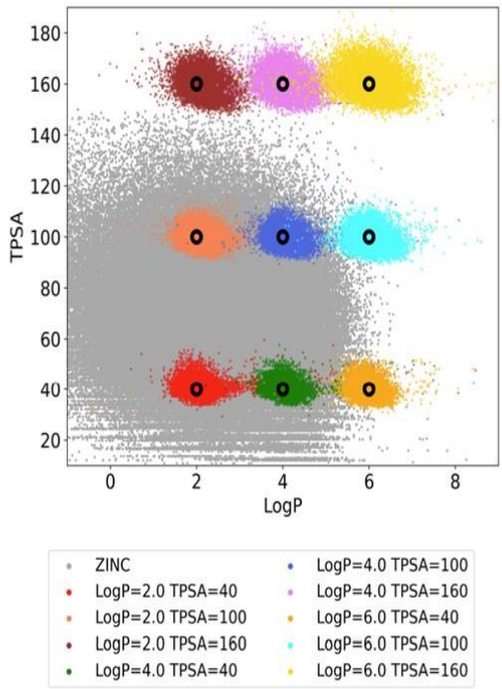


Seo et al Adv. Sci. 2206674 (2023)

10

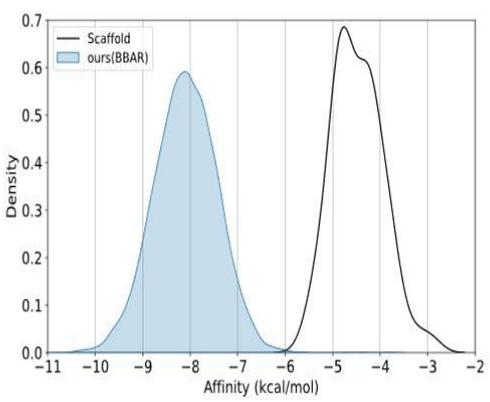
Building block-based generative AI



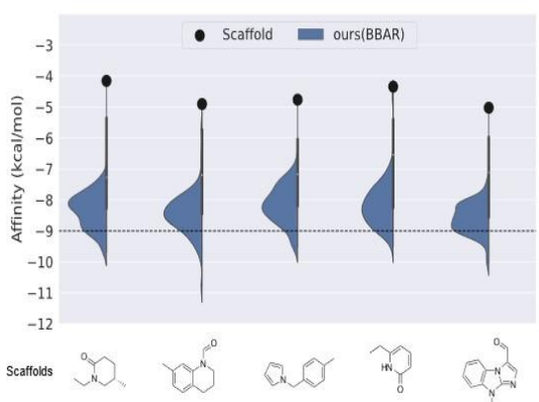


Seo et al Adv. Sci. 2206674 (2023) 11

Design of inhibitors against the 3CL Protease of SARS-CoV-2

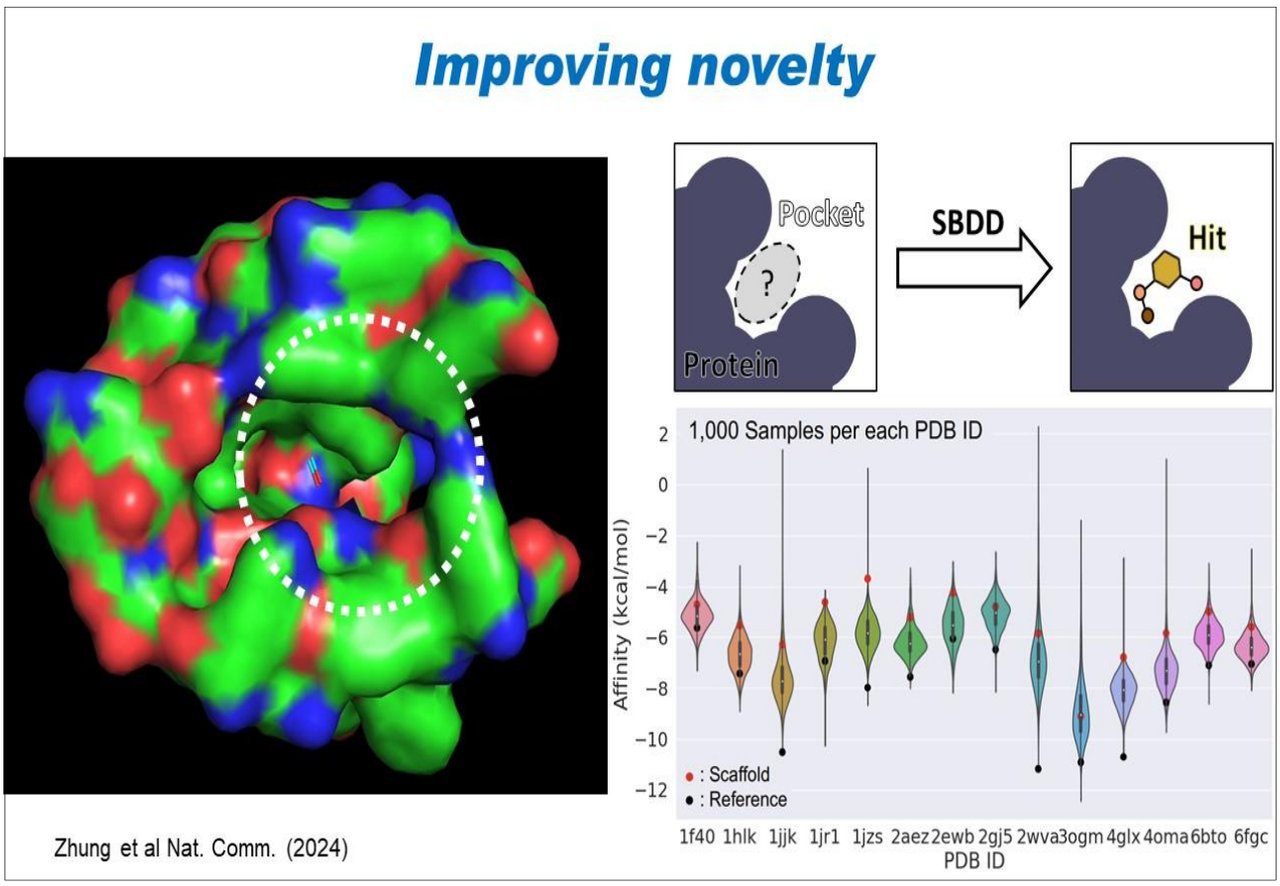


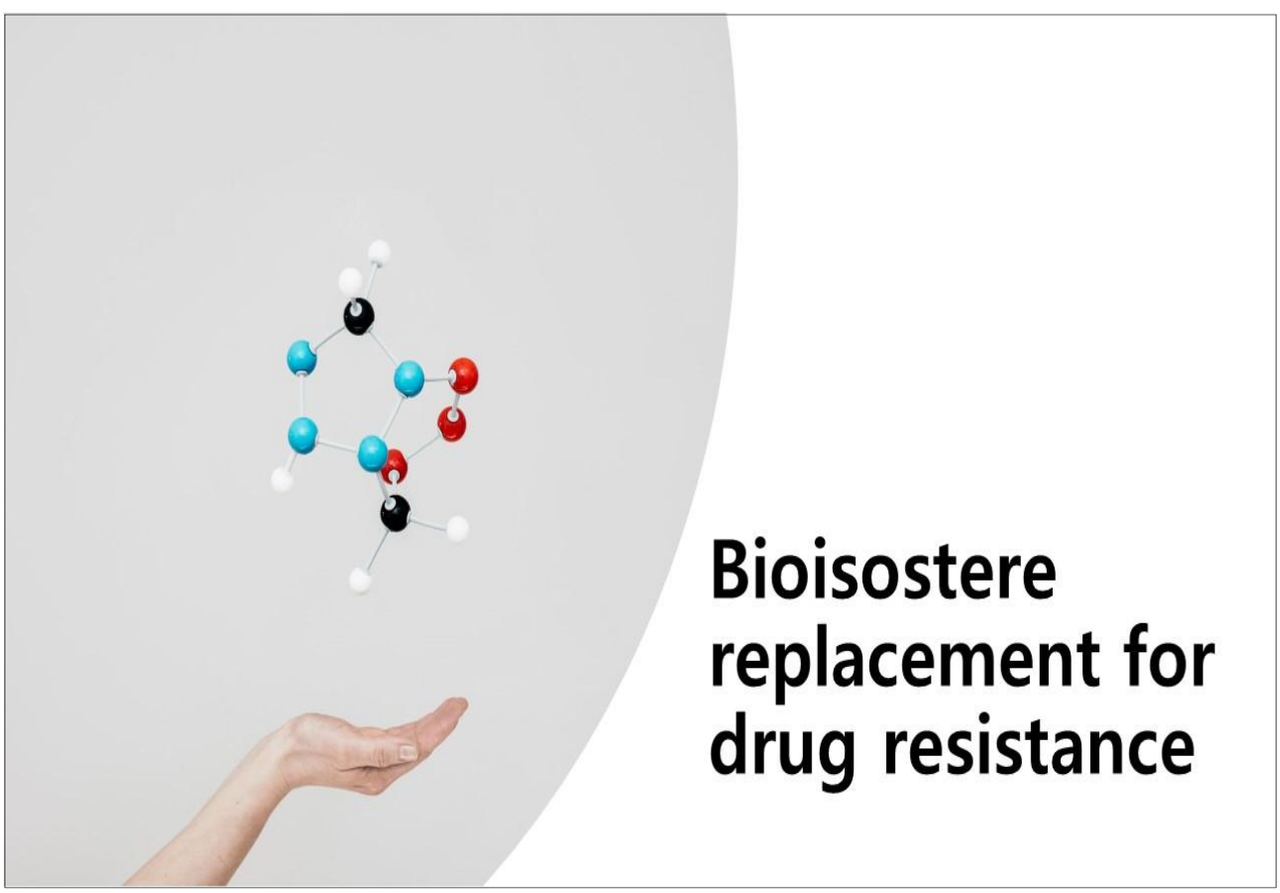
Adv. Sci. 10, 2206674 (2023).



Docking score distributions of the training set (ZINC), the start core structures (scaffold), and the molecules generated by our model(BBAR)

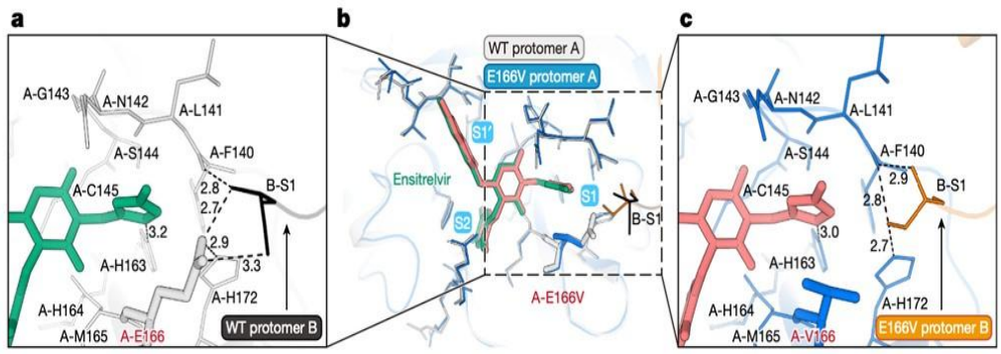
12


Improving novelty
Pocket
?
Protein
SBDD
Hit
1,000 Samples per each PDB ID
Affinity (kcal/mol)
2
0
−2
−4
−6
−8
−10
−12
: Scaffold
: Reference
1f40 1hlk 1jjk 1jr1 1jzs 2aez 2ewb 2gj5 2wva 3ogm 4glx 4oma 6bto 6fgc
PDB ID
Zhung et al Nat. Comm. (2024)


Bioisostere
replacement for
drug resistance

Drug optimization for a mutant with resistance

Ensitrelvir shows drug resistance on the COVID-19 E166V mutant.

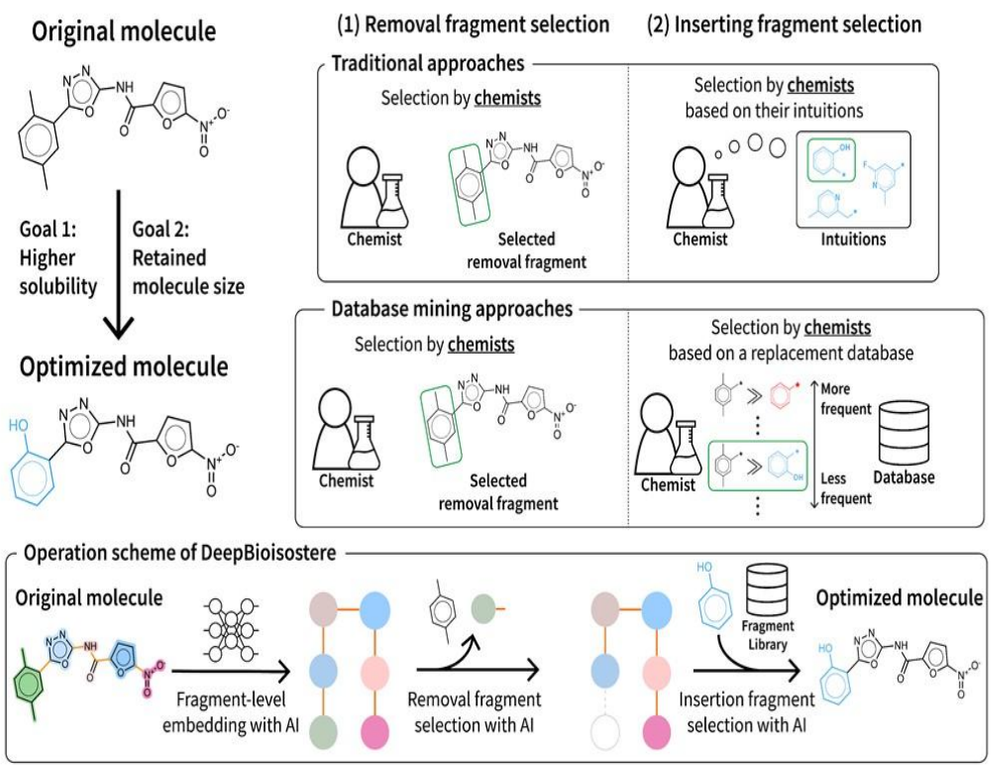


- *Ensitrelvir* is an oral SARS-CoV-2 Main protease inhibitor in a clinical study for treating COVID-19.[1]
- The molecular mechanism of resistance to Ensitrelvir of a mutant E166V has been reported.[2]
- Point mutation: E: Glutamic acid(with minus charge) → V: Valine(hydrophobic).
- No significant change in pocket volume

[1] Unoh, Yuto, et al. "Discovery of S-217622, a noncovalent oral SARS-CoV-2 3CL protease inhibitor clinical candidate for treating COVID-19." *Journal of medicinal chemistry* 65.9 (2022): 6499-6512.
[2] Duan, Yinkai, et al. "Molecular mechanisms of SARS-CoV-2 resistance to nirmatrelvir." *Nature* 622.7982 (2023): 376-382.

15

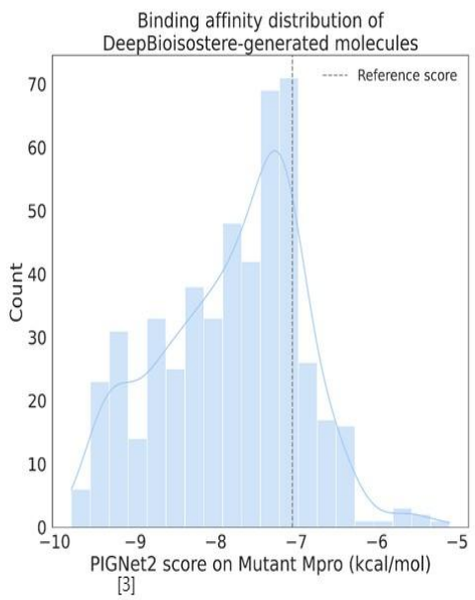
AI for Bioisostere replacement

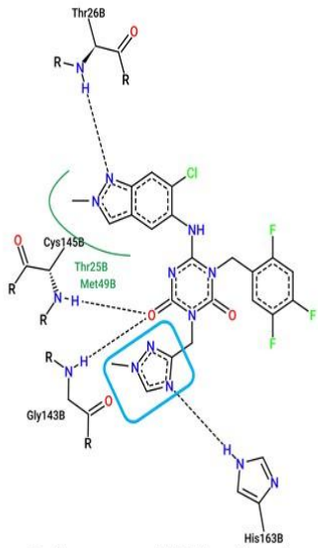


16

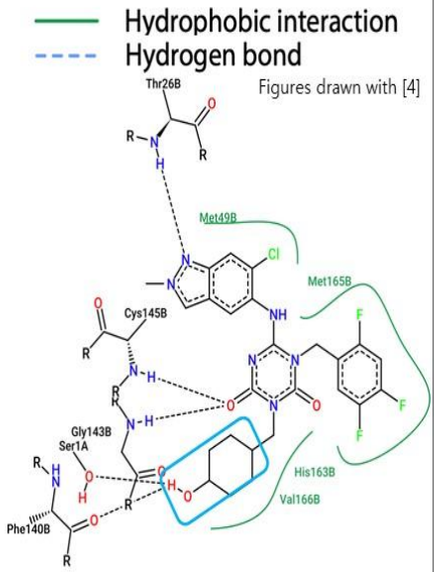
Drug optimization for a mutant with resistance

By optimizing *Ensitrelvir*(reference) with DeepBioisostere, 129 out of 500 molecules showed 10-fold better binding affinity in terms of inhibitory concentration on the E166V mutant.





Reference: -7.05kcal/mol
(Experiment: -8.33kcal/mol)



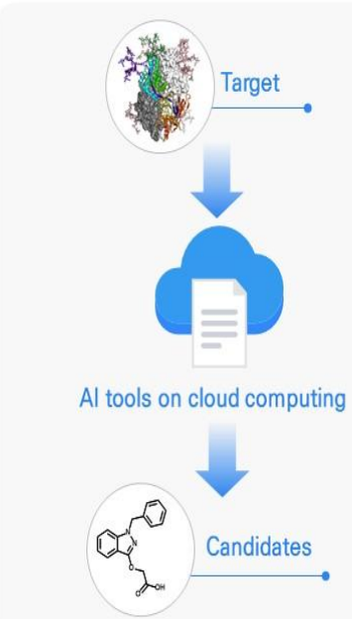
Optimized molecule: -9.66kcal/mol

[3] Moon, Seokhyun, et al. "PIGNet2: a versatile deep learning-based protein–ligand interaction prediction model for binding affinity scoring and virtual screening." *Digital Discovery* (2024).
[4] Stierand, Katrin, and Matthias Rarey. "PoseView--molecular interaction patterns at a glance." *Journal of cheminformatics* 2.1 (2010): 1-1.

17

Advantages of SaaS

- **Accessibility & Collaboration:** easily accessible to researchers worldwide and democratizing advanced AI tools with remote collaboration capability for accelerated drug discovery
- **Flexibility & Customization:** offering specific needs and preferences of end users, allowing for customized workflows to support diverse projects
- **Integrity & Security:** leveraging robust integrity & security to protect sensitive research data from various projects
- **Cost-Effective & Scalability:** cost-effective alternative to on-premise infrastructure by eliminating the need for significant upfront investments in hardware and individual software tools and offering scalable computing power on demand



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Hyper Lab as AI SaaS platform

✓ On-premise SW

- Docking
  - Glide
  - Flare
  - Cresset
- Molecular design
  - Spark
  - Synthia
- Protein structure
  - AlphaFold
- Similarity searching
  - Swiss
  - Scifinder
- Electronic note
  - Dotmatics
  - Scilligence

HYPER LAB

AI + Cloud Integrated solution

✓ SaaS based R&D innovation

- Customized workflow
- Data integrity & utilization
- AI-powered R&D process
- Remote collaboration
- Robust security

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Acknowledgements

4 weeks free trial

- NRF-Korea
- Samsung
- Hanwha
- MFDS

- https://wooyoun.kaist.ac.kr/
- https://hits.ai/
- https://hyperlab.ai/

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세션 3.

신종감염병 백신개발 우수성과

Chair

Baik-Lin Seong

- Yonsei University College of Medicine
- Distinguished Professor & Director General, Vaccine Innovative Technology ALliance (VITAL)-Korea

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

01

COVID-19 백신 연구개발 및 성과

변재철 교수
연세대학교

Speaker

Jae-Chul Pyun

- Yonsei University
- Professor

EDUCATION:

- 2001 Saarland University (Dr.rer.nat)
- 1994 Dept. Chemistry, Seoul National Univeristy (M.S)
- 1992 Dept. Chemistry, Seoul National Univeristy (B.S)

PROFESSIONAL EXPERIENCE:

- 2007 ~ present Professor, Yonsei University
- 1999 ~ 2007 Team leader, KIST Europe GmbH
- 1996 ~ 1999 Investigator, Fraunhofer Institute for Biomedical Engineering
- 2018 ~ present Editor-in-Chief, BioChip Journal
- 2019 ~ present Editor-in-Chief, Journal of the Korean Ceramic Society

Topic

Rapid screening of target antigenic sites for SARS-CoV-2 vaccine development using Fv-antibody library

Abstract

The rapid screening of target antigenic sites for SARS-CoV-2 is presented and the application of screened antigenic sites is demonstrated for the vaccine development against SARS-CoV-2. The Fv-antibody represented the antigen binding site of immunoglobulin G (IgG) and the Fv-antibody library was prepared by randomizing the CDR3 through the site-directed mutagenesis. So prepared Fv-antibody library was surface-expressed on the outer membrane of E.coli with the diversity of more than 106 clones/library. From the Fv-antibody library screening, effective immunogenic antigen sequences for the vaccine development could be analyzed within a few weeks. The vaccine development based on the Fv-antibody library was carried out according to the following procedure: (1) Screening of Fv-antibodies against spike protein of SARS-CoV-2 with a high binding affinity (nanomolar KD), (2) Analysis of amino acid sequence of antigenic sites (epitopes) of the screened Fv-antibodies using computer simulation, (3) Vaccine development using protein particles (ferritin) with co-expressed epitopes, (4) Analysis of neutralization efficiency of anti-sera against SARS-CoV-2 infection.

Development of SARS-CoV-2 vaccine using Fv-antibody library

Jae-Chul Pyun

Materials Science & Engineering
Yonsei University

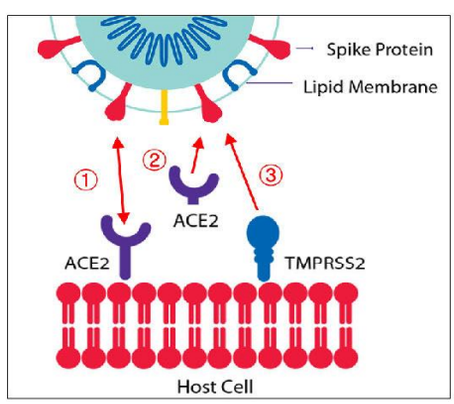
jcpyun@yonsei.ac.kr

보건복지부
Ministry of Health and Welfare

Problems of vaccines against virus

■ **Prevention of viral infection**

① **Antibodies to prevent from binding of virus to host**
② Expressed receptor (fragments) of host cells
③ Inhibition of protease (host cells) for viral infection



■ **Problems**

- **Mutations on viral proteins binding to host receptors**
- **Difficulties to find immunogenic sequence for vaccines**
- **Stability of vaccines (including mRNA vaccines)**

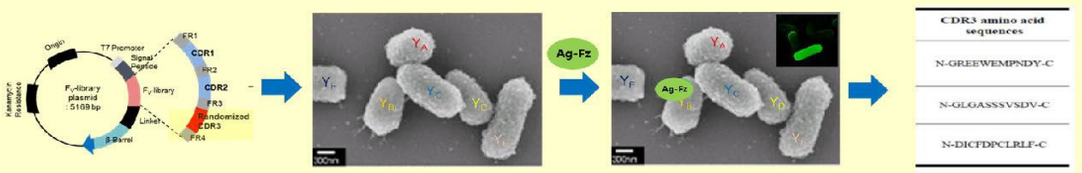
■ **Platforms for vaccine development:**

(1) **Fv-antibody library ⇒ Platform to search immunogenic sequences for vaccines (< 2-3 weeks)**
(2) **Ferritin complex ⇒ Platform of (protein particle) vaccines with high neutralizing efficiency**

Platforms for vaccine development

YONSEI UNIVERSITY

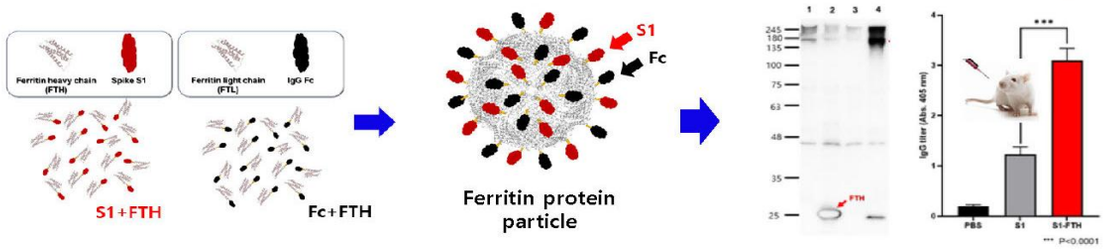
(1) Fv-antibody library: searching platform of immunogenic sequences



- Site-directed mutagenesis of CDR3
- Surface display on E.coli
- Library = $Y_A + Y_B + Y_C + ...$
- Diversity: > 10^7 clones
- Screening with FACS: < 4 h
- Affinity: $K_D > 10^{-9}$ (M)
- Antigenic sequence
- Expression of Fv-antibody

(2) Ferritin protein particle: efficient vaccine platform

C&V



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Fv-antibody library

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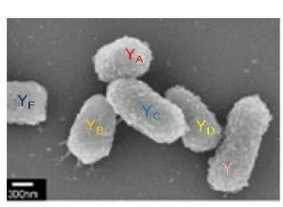
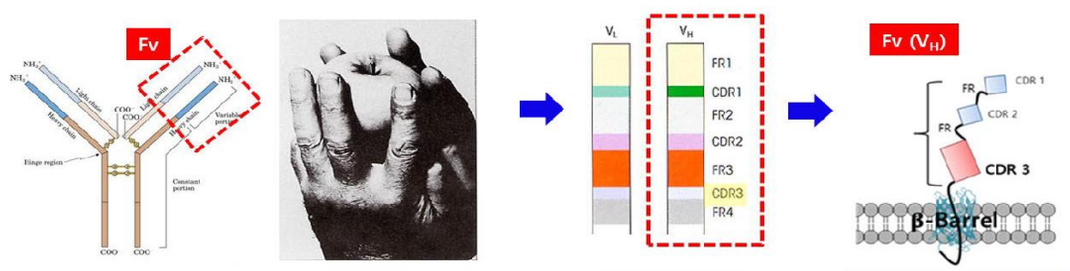
■ Fv-antibody library

- **Fv-antibody**: antigen binding site of IgG (3 CDR's + 4 FR's)
- **Fv-antibody library**: randomizing amino acid sequences of CDR3
- **Surface display**: expression of Fv-antibodies on the outer membrane (OM) of E.coli with high surface density
- **Surface density: >10^5 (Fv/E.coli cell), Expression yield: >95 %**

(비교) Bacteriophage: Surface density >10 (Fv/phage), yield <10 %



- 항체라이브러리 = $Y_A + Y_B + Y_C + \cdots\cdot$
- 최종 항체다양성: > 10^7 clones



*CDR: complementarity-determining region

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Fv-antibody library

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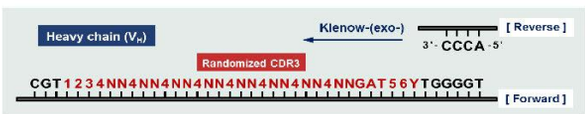
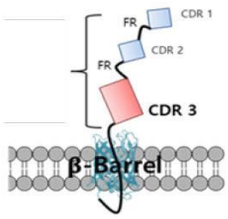
■ **Fv-antibody library**

- **V_{HH}-CDR3: 11 amino acids (33 base)** (V_{HK}-CDR3: 8 amino acids)
- **Randomizing V_{HH}-CDR3** through site-directed mutagenesis

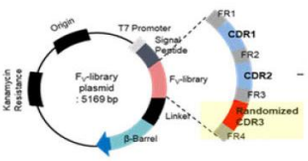


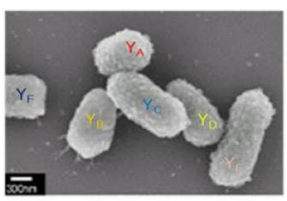
*CDR: complementarity-determining region



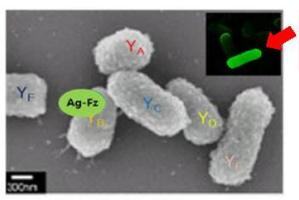
Fv-antibody library (on E.coli cell)

■ **Screening of Fv-antibody library**





Ag-Fz



Target E.coli

- Site-directed mutagenesis of CDR3
- Surface display on E.coli

- Library = $Y_A + Y_B + Y_C + ...$
- Diversity: > 10^7 clones

- Screening with FACS: < 4 h
- Affinity: K_D > 10^{-9} (M^{-1})

Flow-chart for vaccine development

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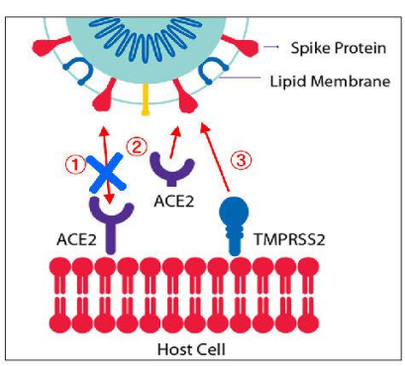
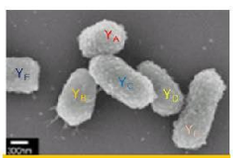
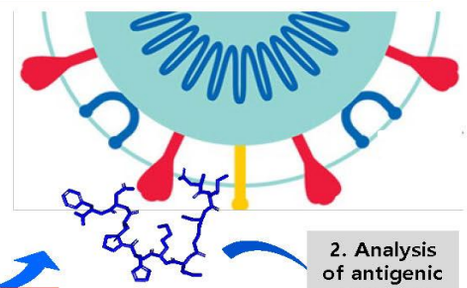




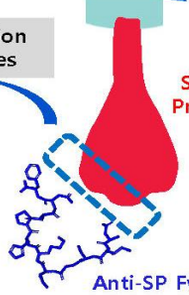
F_V-antibody library

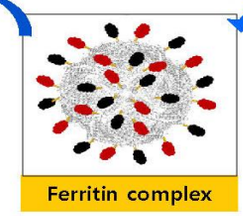
1. Screening



2. Analysis of antigenic sequence

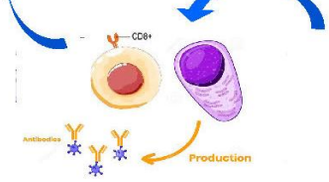
3. Expression of vaccines





4. Vaccination

5. Analysis of neutrality



Screening of anti-RBD(SARS-CoV-2)-Fv

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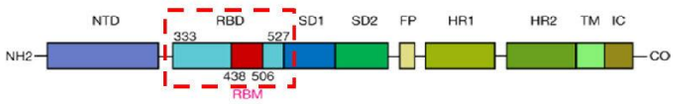
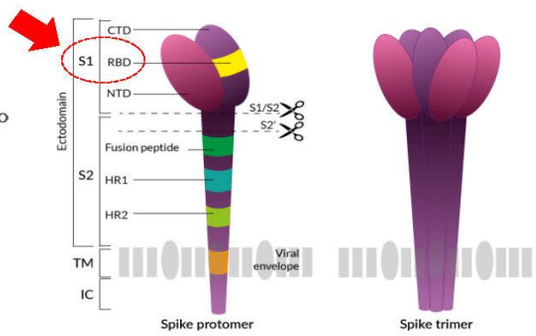
■ Spike protein RBD (SARS-CoV-2)

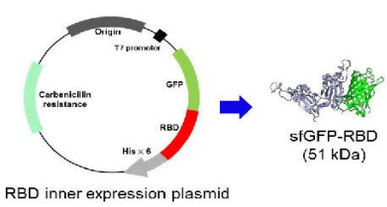




- **RBD (319-541 a.a.):** ACE2 receptor binding domain
- SP (1,273 mer): **RBD (222 mer, 24.9 kDa)**
- **Fluorescence label**: sfGFP

■ RBD (SARS-CoV-2) antigen (searching probe)

RBD of spike protein (319-541)



RBD inner expression plasmid

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Screening of anti-RBD(SARS-CoV-2)-Fv

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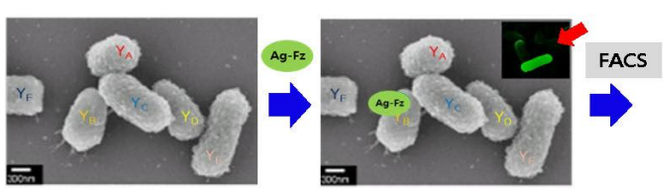
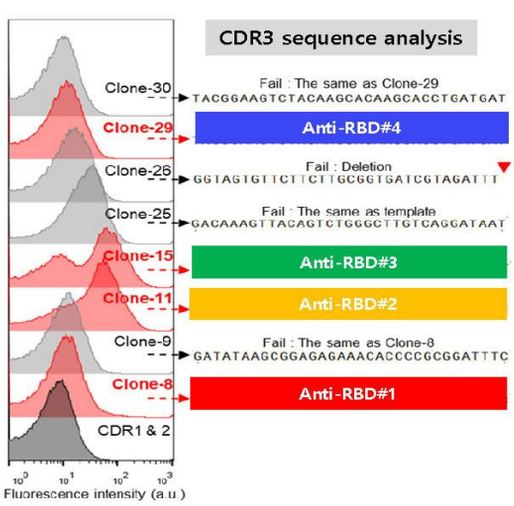
■ Screening with RBD probe (GFP labeled)



- Library = $Y_A + Y_B + Y_C + ...$
- Diversity: > 10^7 clones
- Screening with FACS: < 4 h
- Affinity: $K_D > 10^{-9}$ (M^{-1})

Anti-RBD (Clone#)	Oligonucleotide sequence (33 nucleotides)	CDR3 amino acid sequence (11 aa)
1 (8)	3'-GCT CGT GXX AXX AXX GXX GXX AXX CXX CXX GXX GXX TXX TGG GGT-5'	^{1}DXXXX ^{6}KXXXX ^{11}F
2 (11)	3'-GCT CGT GXX GXX AXX CXX AXX GXX CXX AXX AXX GXX TXX TGG GGT-5'	^{1}DXXXX ^{6}GXXXX ^{11}F
3 (15)	3'-GCT CGT GXX CXX CXX AXX GXX AXX AXX GXX AXX GXX TXX TGG GGT-5'	^{1}DXXXX ^{6}TXXXX ^{11}F
4 (29)	3'-GCT CGT TXX GXX AXX CXX CXX GXX CXX GXX CXX GXX GXX TGG GGT-5'	^{1}YXXXX ^{6}AXXXX ^{11}D



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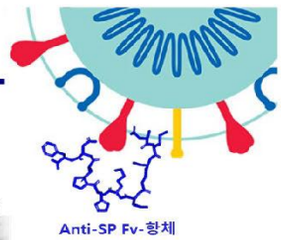
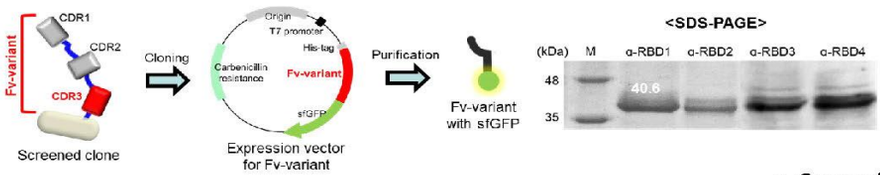
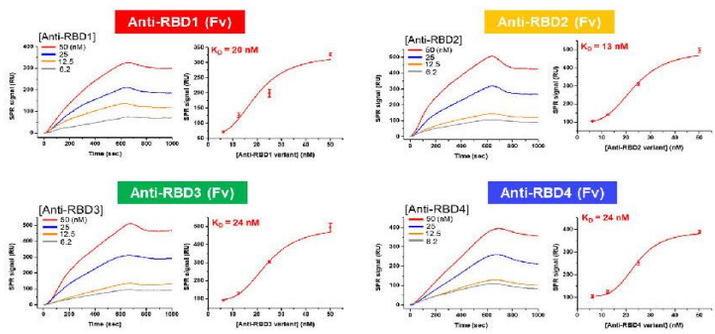
Binding affinity of anti-RBD(SARS-CoV-2)-Fv



■ **Expression of Fv-antibody (soluble)**



■ **Estimation of binding affinity (SPR biosensor, K_D)**



< Comparison of binding affinity >

α-RBD#	LOD (nM)	K_D (nM)
SP (SARS-CoV-1) to ACE2 receptor		31 – 100*
SP (SARS-CoV-2) to ACE2 receptor		4.7 – 10*
α-RBD#1	7.7	20
α-RBD#2	7.7	13
α-RBD#3	8.7	24
α-RBD#4	13.73	24

* Nature, **581** (2020) 215–220

Flow-chart for vaccine development

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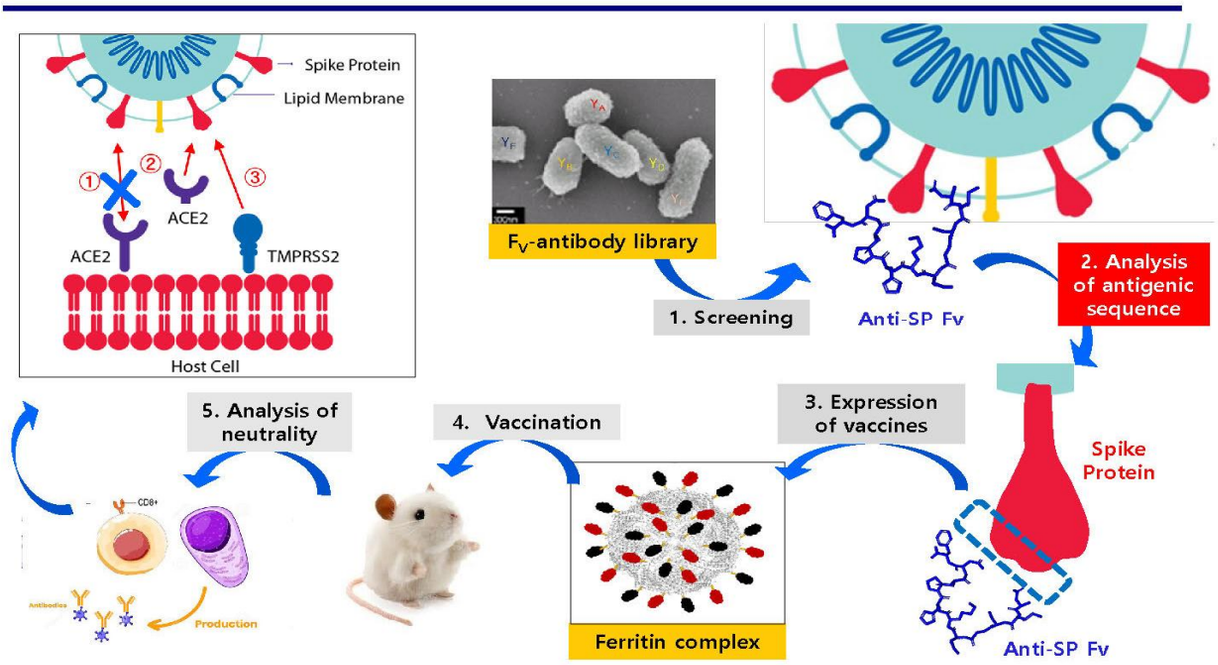

Docking analysis of anti-RBD(SARS-CoV-2)-Fv

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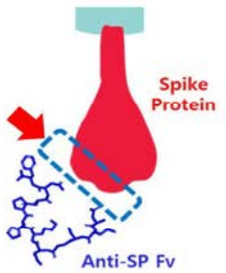
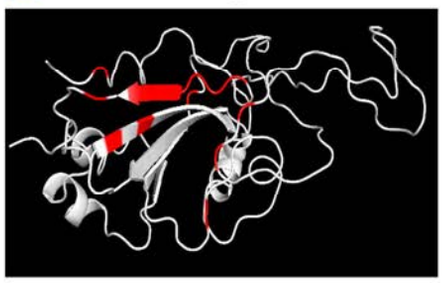


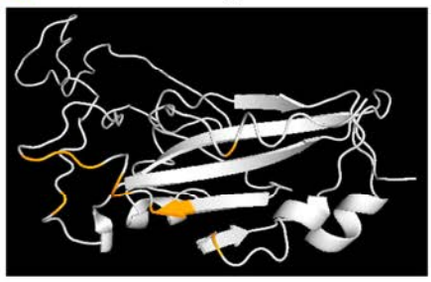
α-RBD#	LOD (nM)	K_D (nM)
SARS-CoV-1 to ACE2 receptor		31 – 100*
SARS-CoV-2 to ACE2 receptor		4.7 – 10*
α-RBD.1	7.7	20
α-RBD2	7.7	13
α-RBD3	8.7	24
α-RBD4	13.73	24

* Nature, **581** (2020) 215–220

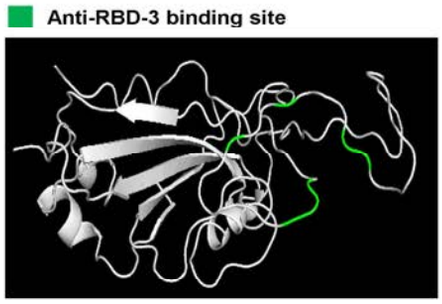
Anti-RBD-1 binding site



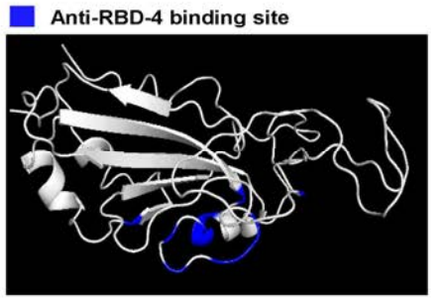
Anti-RBD-2 binding site



Anti-RBD-3 binding site



Anti-RBD-4 binding site



Antigenic sequences of anti-RBD-Fv

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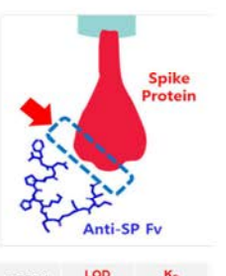
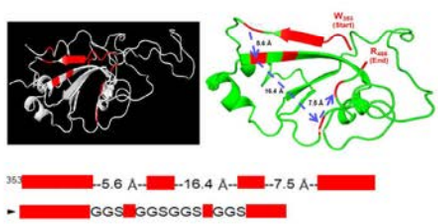


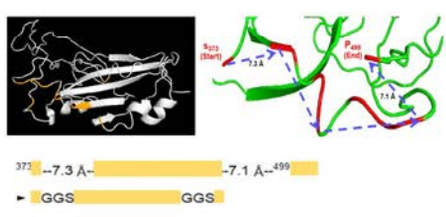
α-RBD#	LOD (nM)	K_D (nM)
SARS-CoV-1 to ACE2 receptor		31 – 100*
SARS-CoV-2 to ACE2 receptor		4.7 – 10*
α-RBD.1	7.7	20
α-RBD2	7.7	13
α-RBD3	8.7	24
α-RBD4	13.73	24

* Nature, **581** (2020) 215–220

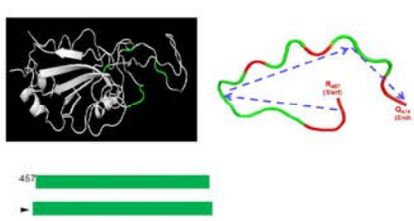
Anti-RBD-1 binding site



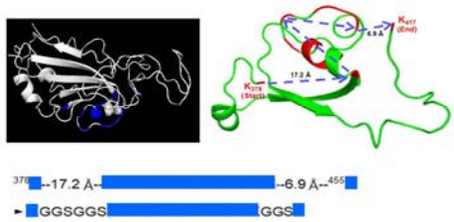
Anti-RBD-2 binding site



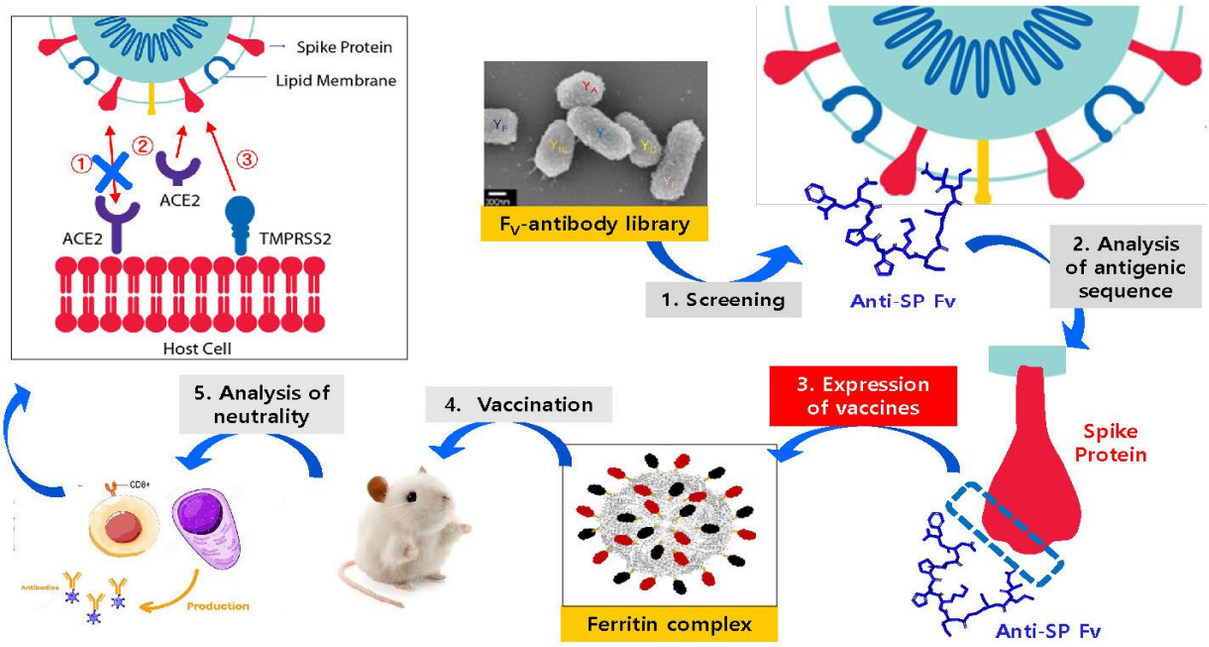
Anti-RBD-3 binding site



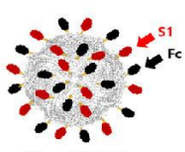
Anti-RBD-4 binding site



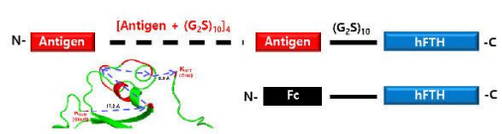
Flow-chart for vaccine development



Ferritin complex with antigenic sequences

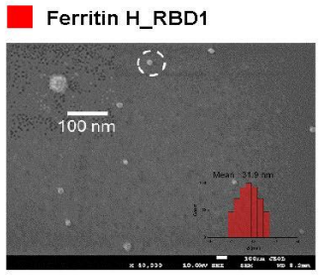


- hFTH (192 mer, 24.8 kDa)
- Antigen1~4 = (ca.2.4 kDa)
- $(G_2S)_{10}$ = 2 kDa
- Complex = ca. 46 kDa

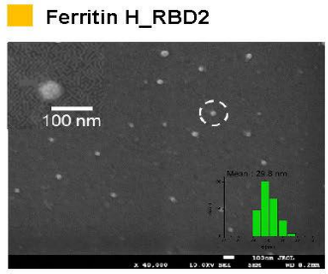


Ferritin H RBD#	Amino acid sequence of RBD antigen (N → C-term)
1	353 --5.6 Å-- --16.4 Å-- --7.5 Å-- GGS GGSGGS GGS
2	373 --7.3 Å-- --7.1 Å-- 499 GGS GGS
3	457
4	376 --17.2 Å-- --6.9 Å-- 455 GGSGGS GGS

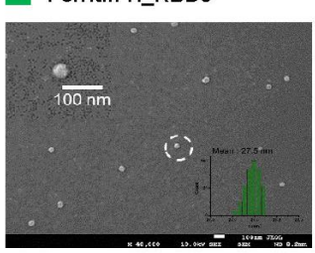
Ferritin H_RBD1



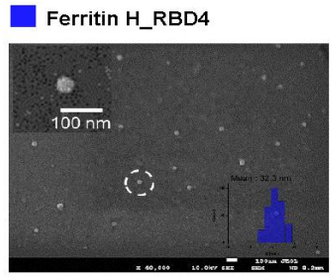
Ferritin H_RBD2



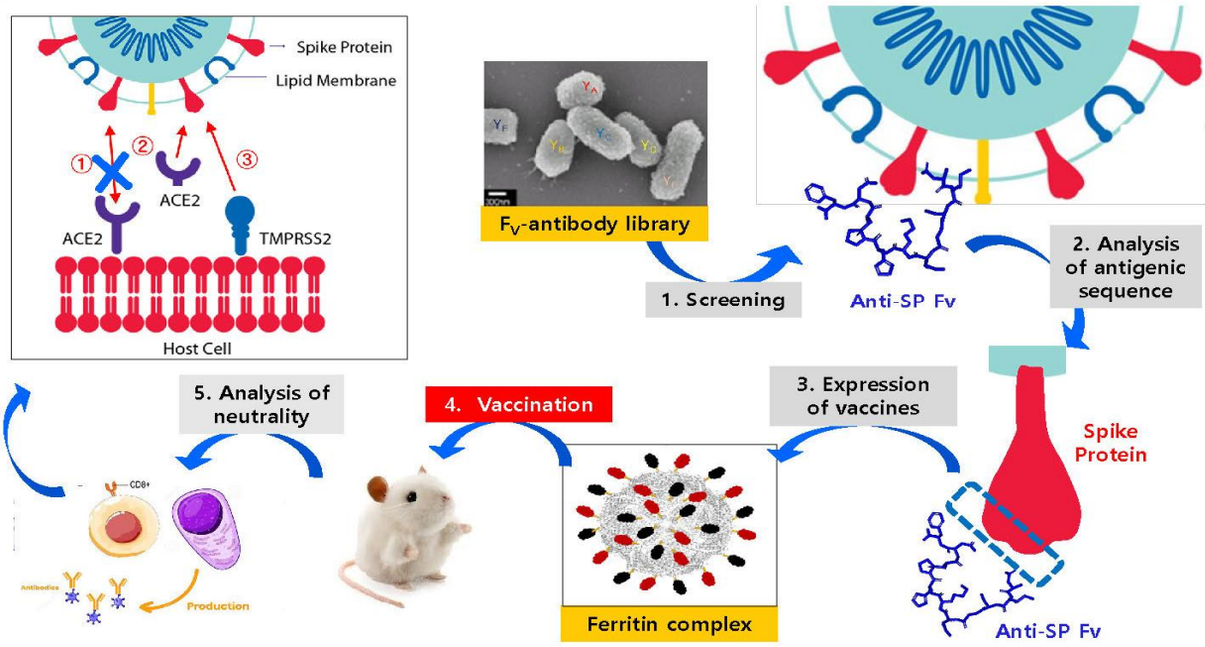
Ferritin H_RBD3



Ferritin H_RBD4



Flow-chart for vaccine development



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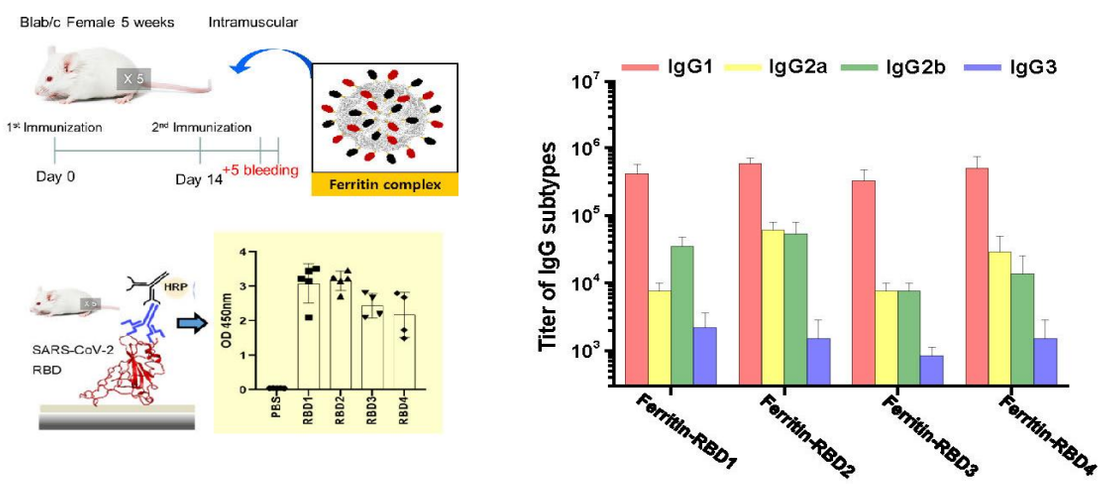
Vaccination with ferritin complex

■ **Vaccination and characterization of anti-sera**

- **Analysis of IgG titer and neutrality of anti-sera**
- Subtyping of **IgG1(Th2, IL-4-cytokine-supporting) and IgG2, 3(Th1, IFN-γ-controlling)**



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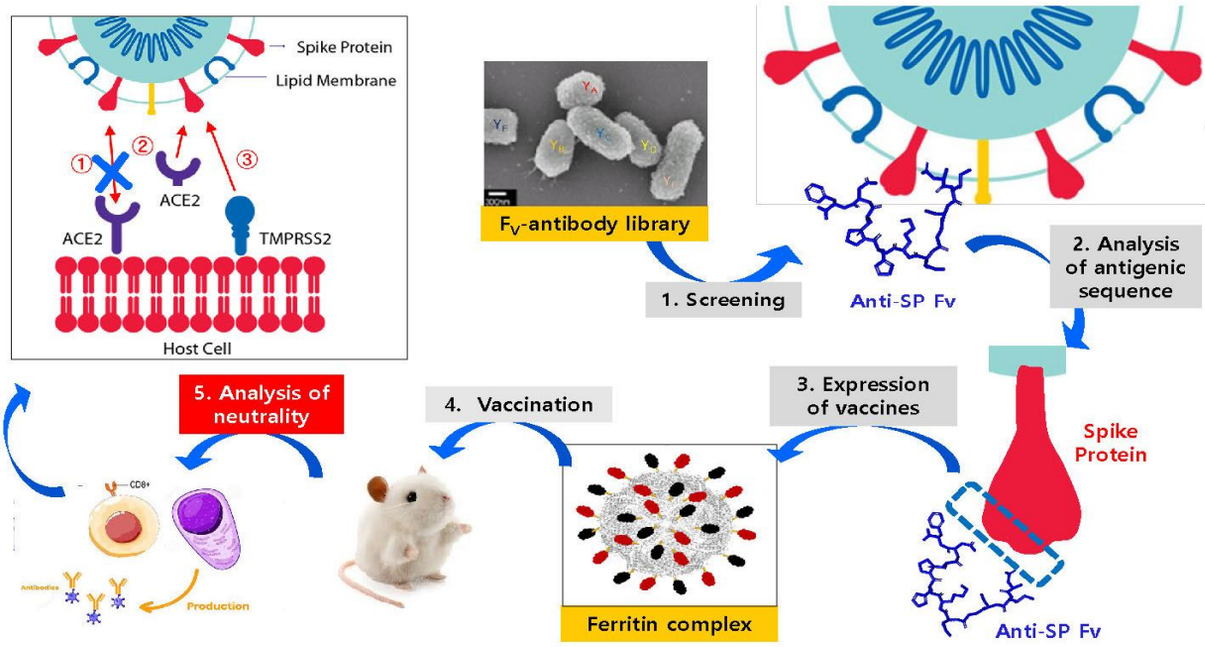
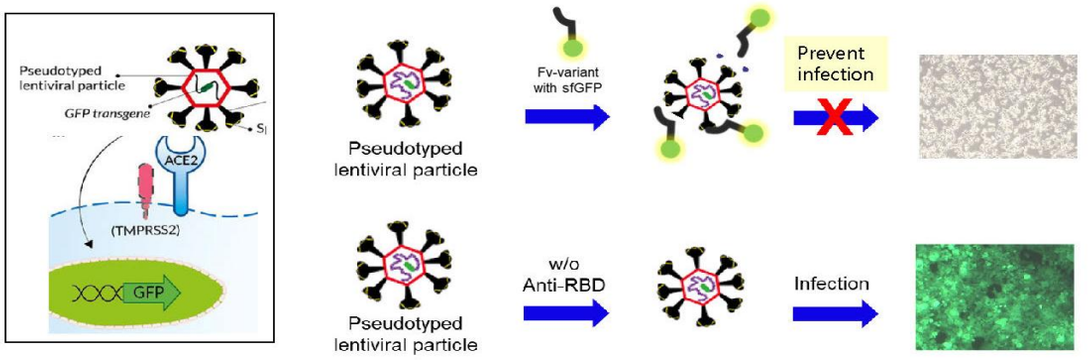
Flow-chart for vaccine development



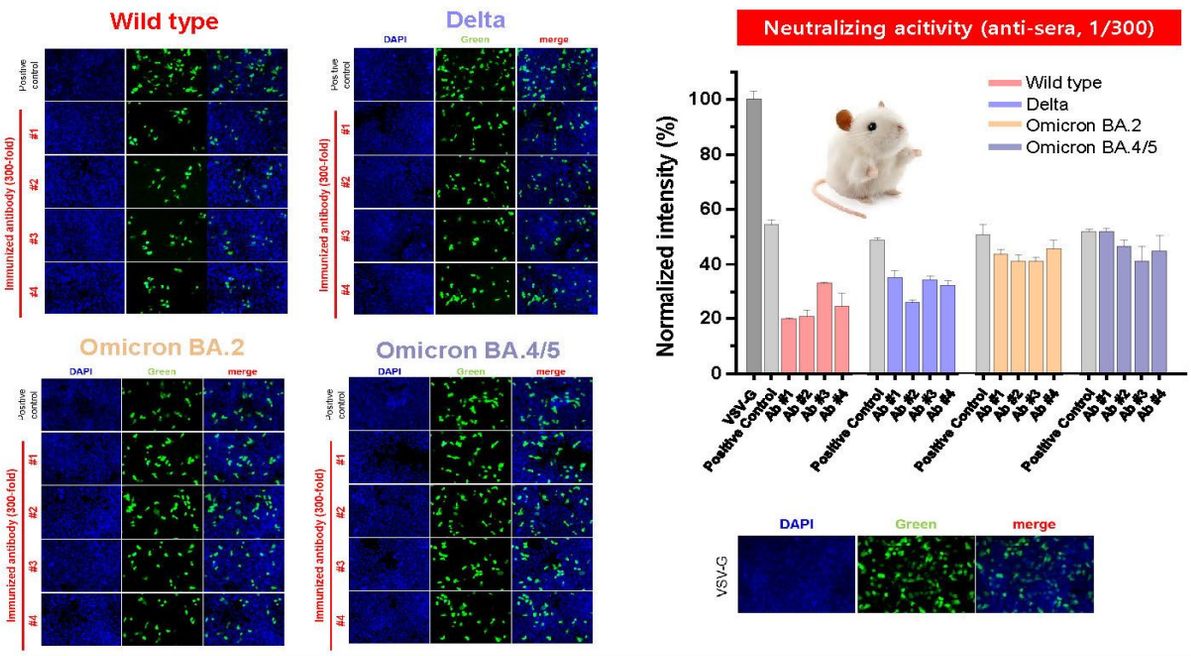
Neutralizing activity assay (in-vitro)

■ **Netralizing activity assay (in-vitro)**

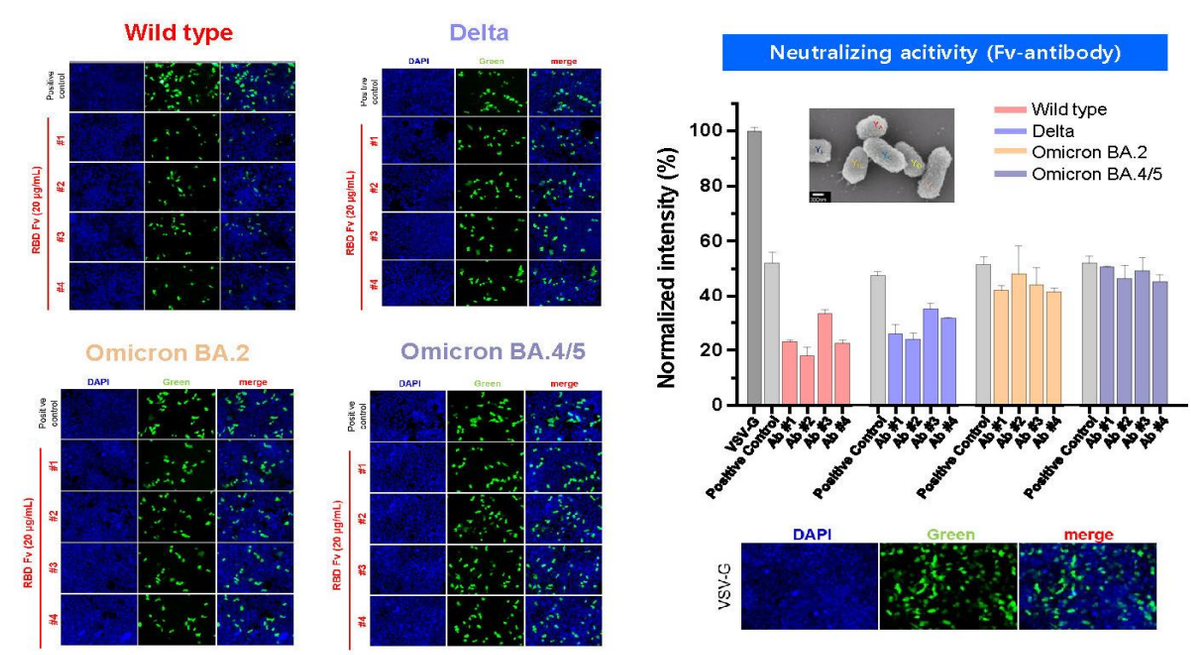
- **Pseudo-virus particle (Takara, Invivogen)**
  - Leti-virus with SARS-CoV-2 SP (original)
  - **GFP gene as an indicator**
  - Variants with mutated SARS-CoV-2 SP
- **Infection reporter cell lines (Invivogen)**
  - Cell lines with overexpressed ACE2 & TMPRSS2
  - **Fluorescence signaling after infection of SARS-CoV-2**



Neutralizing activity (anti-sera to variants)

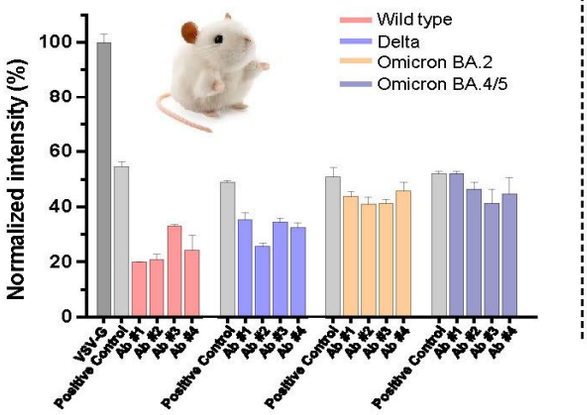


Neutralizing activity (Fv-antibodies to variants)

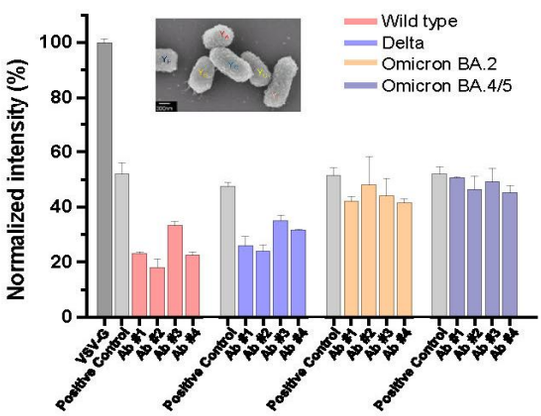


Comparison with neutralizing activity (Anti-sera vs. Fv-antibodies)

Neutralizing acitivity (anti-sera)



Neutralizing acitivity (Fv-antibody)



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Screening of Fv-antibodies against SARS-CoV-2

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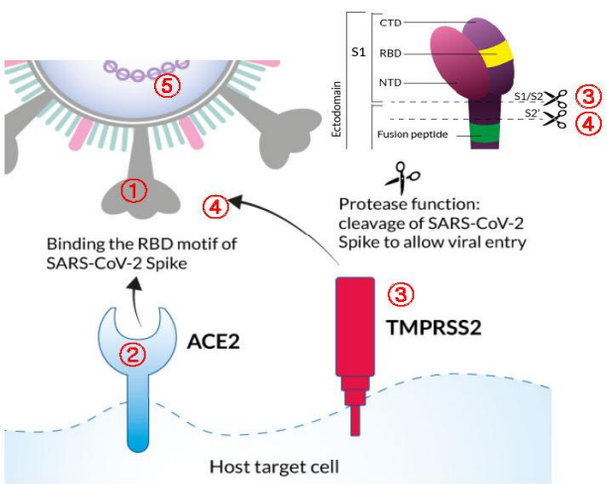
1. Anti-RBD(SP)-Fv
2. Anti-ACE2-Fv
3. Anti-TMPRSS2 Fv (to inhibit protease activity)
4. Anti-PPC site-Fv
5. Anti-NP-Fv
6. RNase Inhibitors (to stabilize mRNA vaccines)



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Acknowledgement

This work was supported by Global Vaccine Leading Technology Center Program through the Korea Health Industry Development Institute (KHIDI) and by Basic Science Research Program through the National Research Foundation (NRF) of Korea.

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Development of SARS-CoV-2 vaccines using Fv-antibody library

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Materials Science & Engineering
Yonsei University

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보건복지부
Ministry of Health and Welfare

02

인플루엔자 백신 연구개발 및 성과

김진일 교수
고려대학교

Speaker

Jin-Il Kim

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- Associate Professor

EDUCATION:

- 2016 Visiting Scholar, Rega Institute
  KU Leuven – University of Leuven (Leuven, Belgium; Prof. Philippe Lemey)
- 2018 Research professor, Institute for Viral Diseases
  Korea University College of Medicine
- 2014 Doctor, Virology
  College of Medicine, Hallym University
- 2012 Master, Virology
  College of Medicine, Hallym University
- 2009 Bachelor, Veterinary Medicine
  College of Veterinary Medicine, Chungnam National University

PROFESSIONAL EXPERIENCE:

- 2021 ~ Current Associate Professor
  Department of Microbiology, Korea University College of Medicine (Seoul, Republic of Korea)
- 2018 ~ 2021 Assistant Professor
  Department of Microbiology, Korea University College of Medicine (Seoul, Republic of Korea)
- 2020 ~ 2021 Chair, International Relations, the Korea Society of Virology (KSV; Republic of Korea)
- 2018 ~ Current Member, the Councilor Board, the Korea Society of Virology (KSV; Republic of Korea)
- 2014 ~ Current Member, the American Society for Virology (ASV; USA)

Topic

HAs-NAu strategy for the development of better influenza vaccines

Abstract

Even though we have managed our lives by dealing with pandemic viruses, another will come to test what we have prepared against it. Highly pathogenic avian influenza A(H5Nx) viruses may be on top of potential pandemic viruses in the future. As we may know, the influenza A virus (IAV) can infect various animal hosts, and the IAV goes through genetic drift and shift. Hence, different subtypes and antigenic IAVs are circulating simultaneously in nature. It will be one of the reasons that we need a universal influenza vaccine. However, it is difficult that subdominant but cross-reactive epitopes found in the stem region of hemagglutinin (HA), one of the two major surface glycoproteins in the viral envelope, are utilized sufficiently in any conventional influenza vaccine platform. To this end, mRNA or recombinant protein strategies of COVID-19 vaccines can be a breakthrough for developing universal influenza vaccines because, using either vaccine strategy, vaccine antigen contents can be manipulated. The HA antigen may deliver protection against seasonal influenza viruses, and neuraminidase (NA), another surface glycoprotein of IAVs, may work as a universal vaccine antigen because the NA evolves genetically slower than the HA. In this regard, a universal NA vaccine antigen can be designed even for avian H5Nx viruses.

HAs-NAu Strategy for the development of better influenza vaccines

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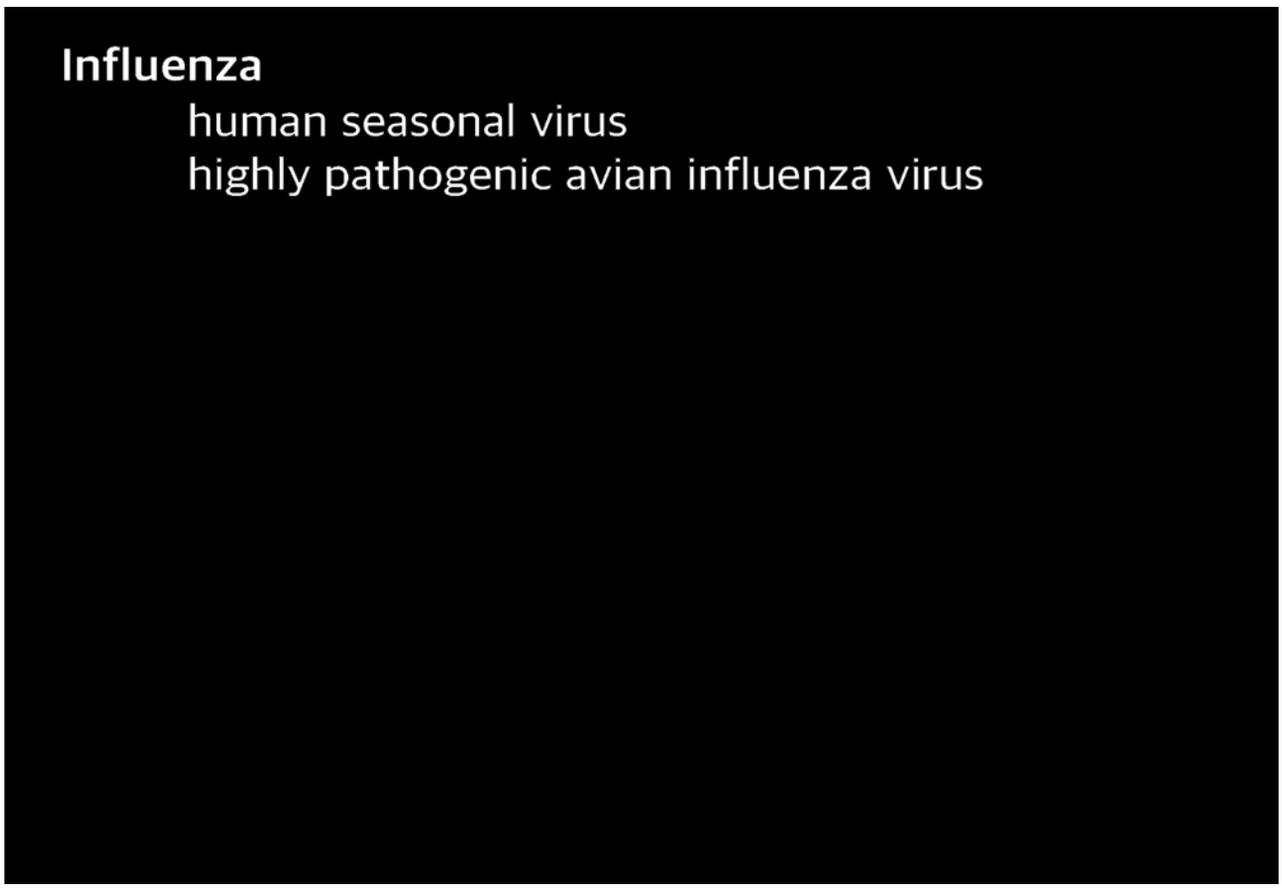
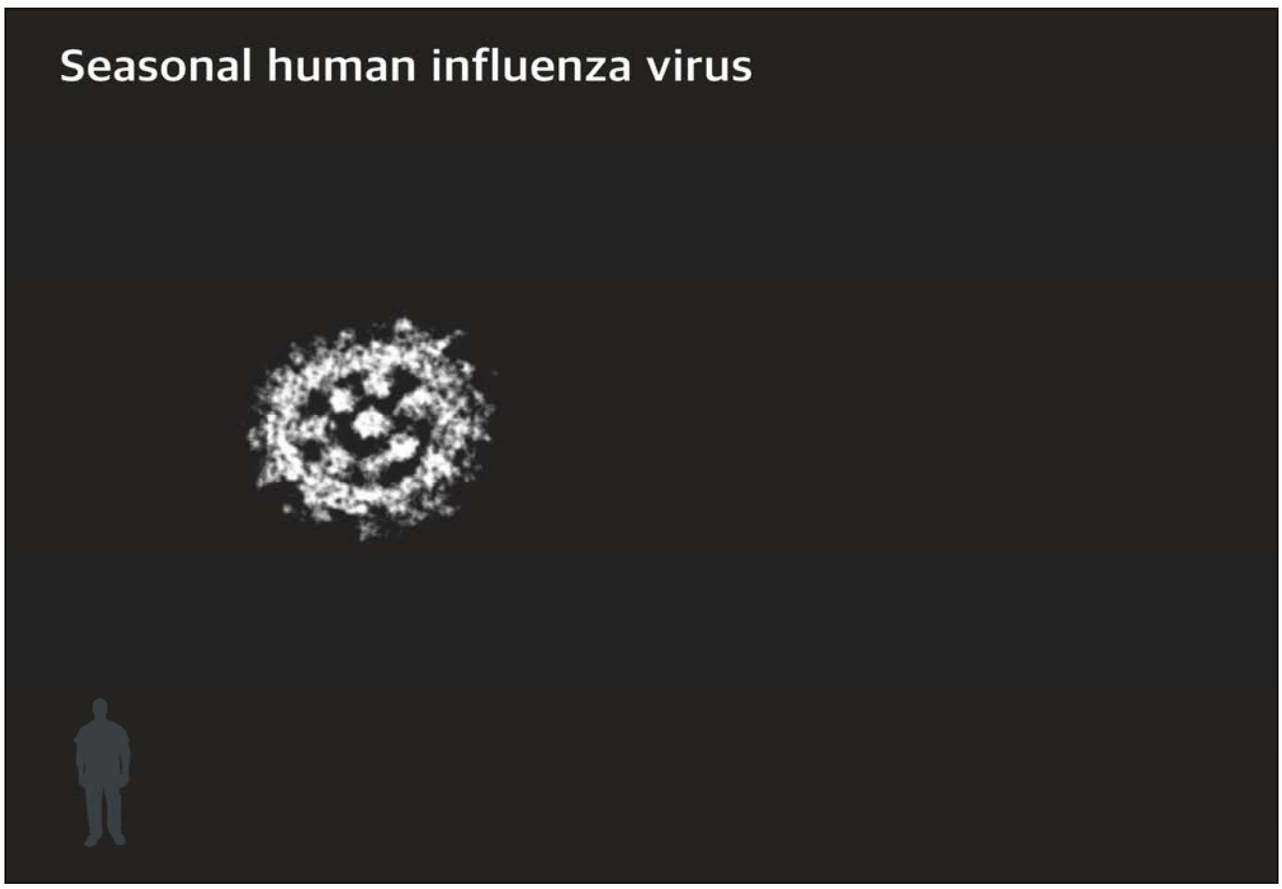
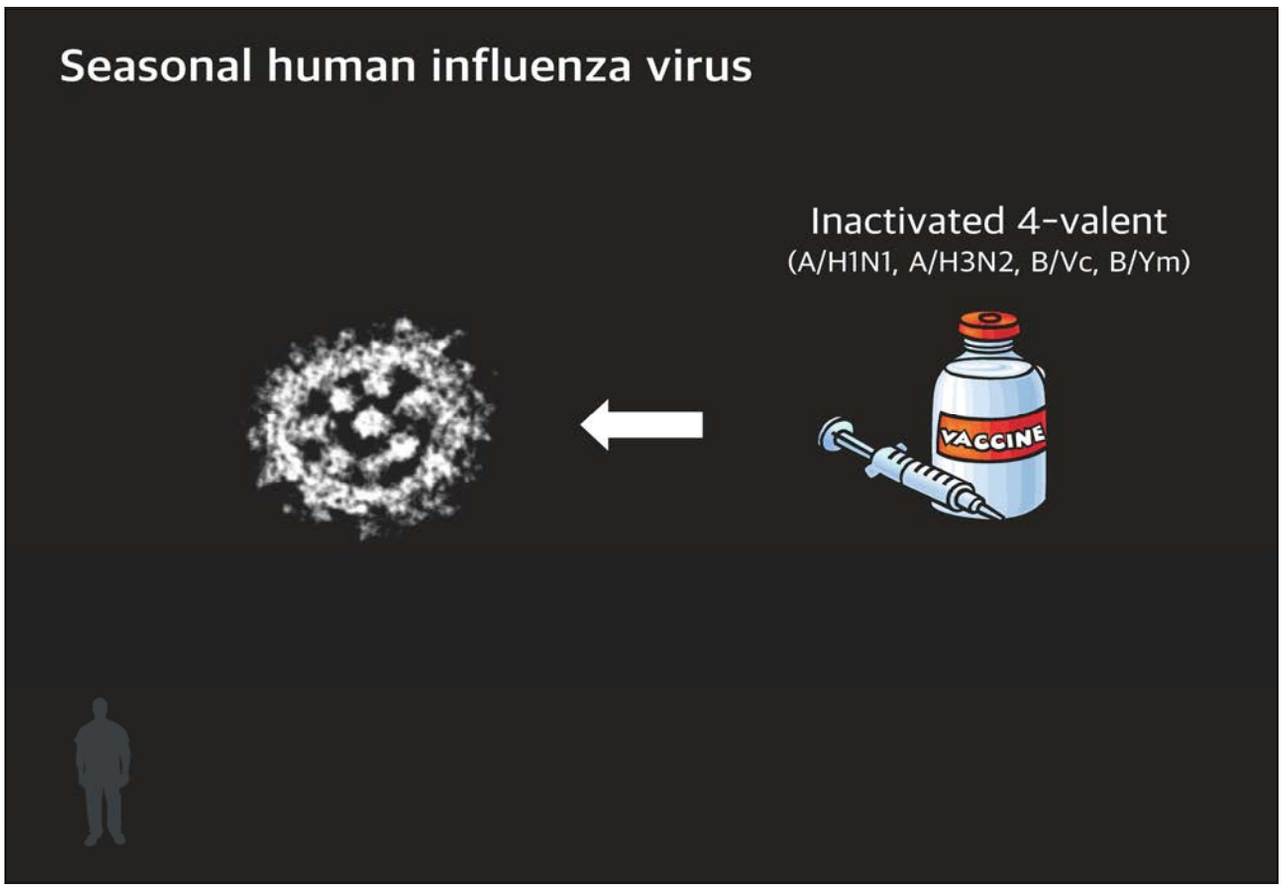
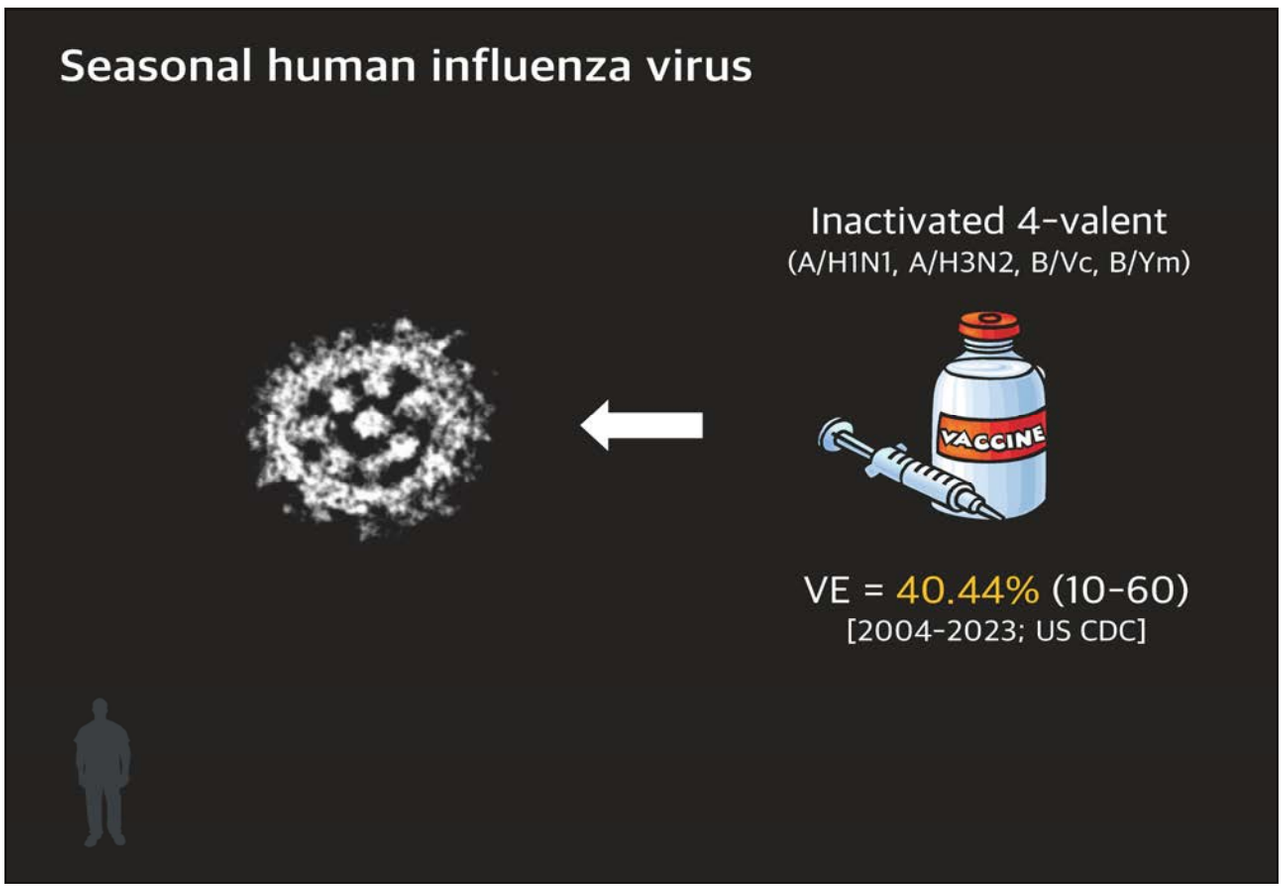
Lab of Viral Molecular Epidemiology
Department of Microbiology
Institute for Viral Diseases
Vaccine Innovation Center
Korea University College of Medicine

Influenza


Influenza
human seasonal virus
highly pathogenic avian influenza virus


Seasonal human influenza virus


Seasonal human influenza virus
Inactivated 4-valent
(A/H1N1, A/H3N2, B/Vc, B/Ym)
VACCINE


Seasonal human influenza virus
Inactivated 4-valent
(A/H1N1, A/H3N2, B/Vc, B/Ym)
VACCINE
VE = 40.44% (10-60)
[2004-2023; US CDC]

Seasonal human influenza virus

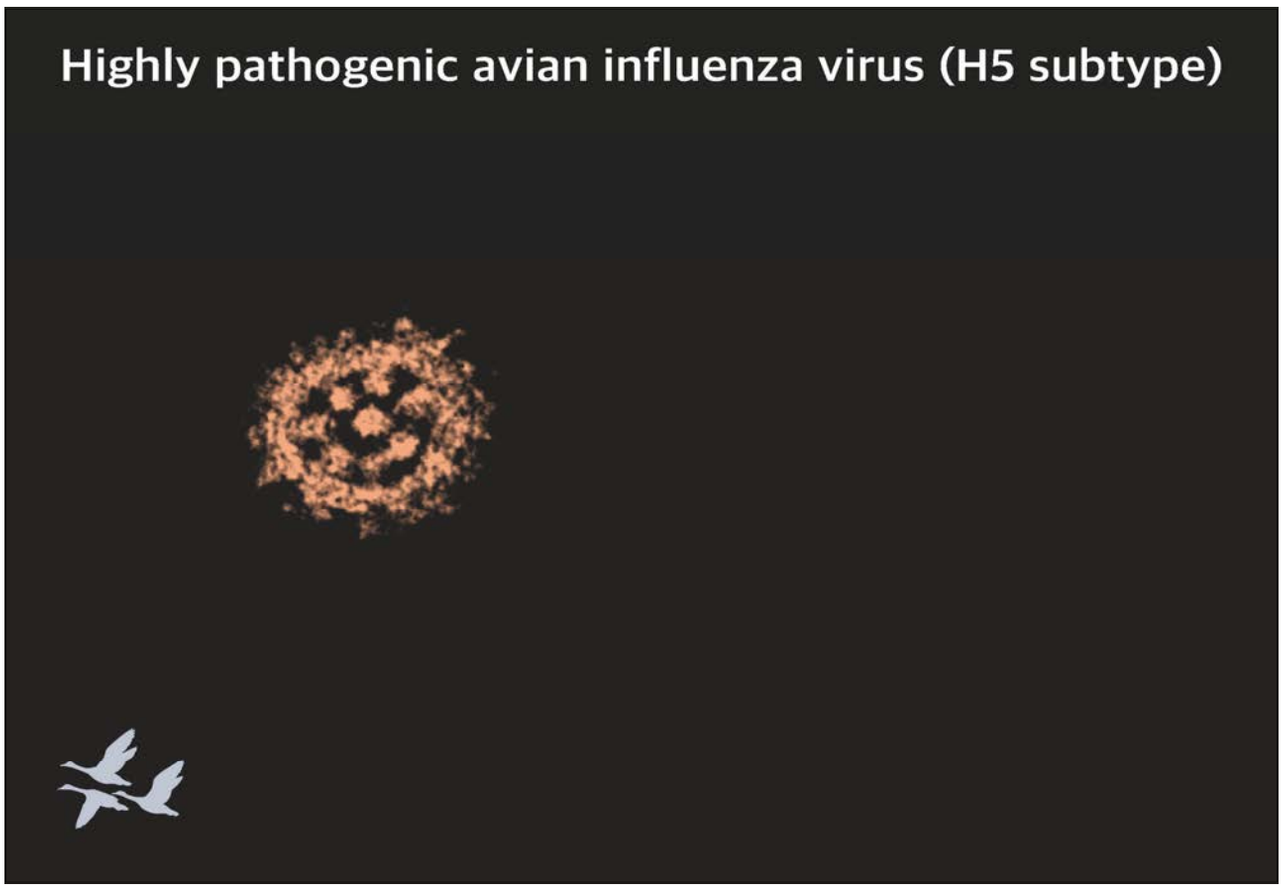
Inactivated 4-valent
(A/H1N1, A/H3N2, B/Vc, B/Ym)

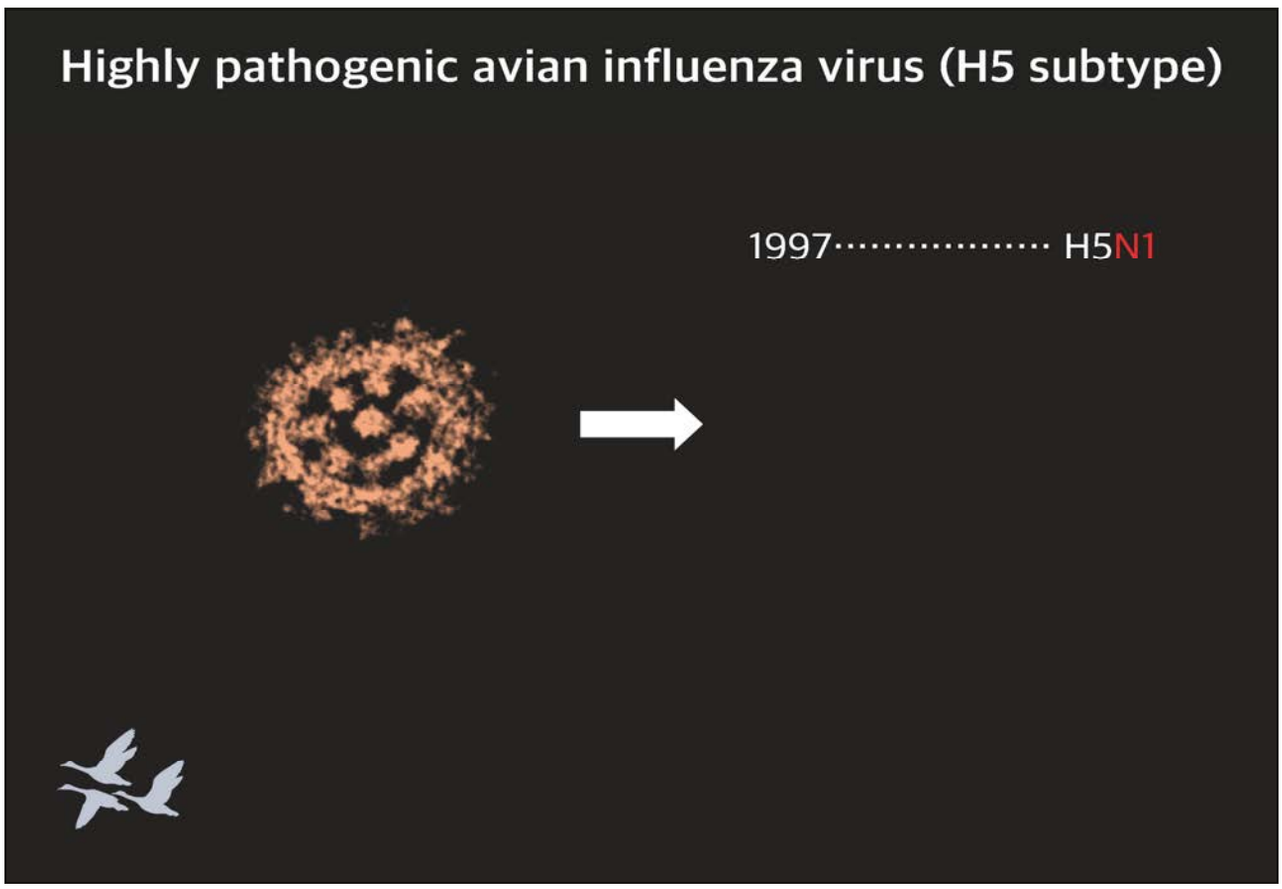
VE = 40.44% (10-60)
[2004-2023; US CDC]

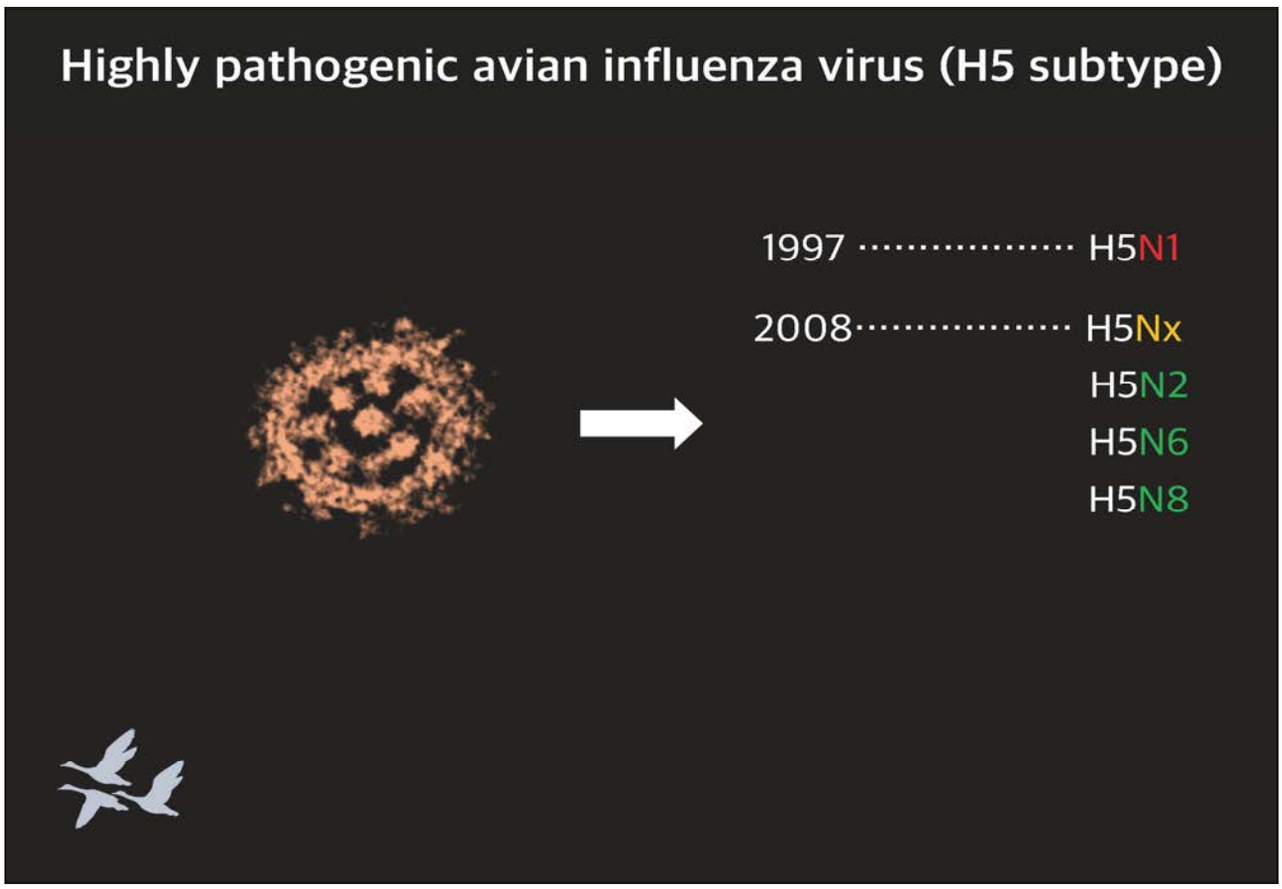
A/H3N2 lowers VE almost every season.

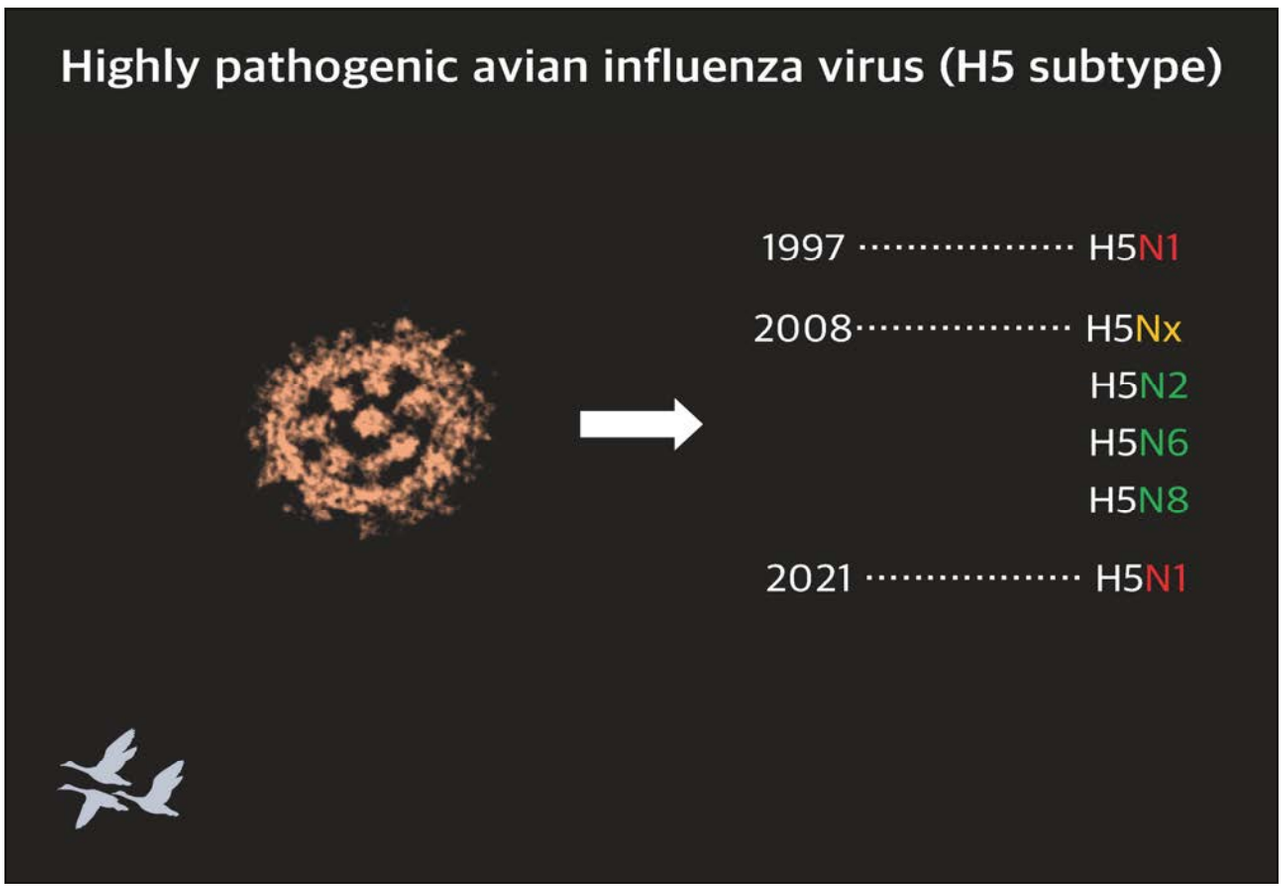
Frequent changes of A/H3N2 vaccine antigens

Season	A/H1N1	A/H3N2	B
1976-1977	A/New Jersey/76	A/Victoria/3/75	B/Hong Kong/5/72
1977-1978			
1978-1979	A/USSR/90/77	A/Texas/1/77	
1979-1980	A/USSR/90/77 or A/Brazil/11/78		
.	.	.	.
.	.	.	.
.	.	.	.
2000-2001	A/New Caledonia/20/1999	A/Moscow/10/99	B/Beijing/184/93
2001-2002			B/Sichuan/379/99
2002-2003			B/Hong Kong/330/2001
2003-2004			
2004-2005		A/Fujian/411/2002	B/Shanghai/361/2002
2005-2006		A/California/7/2004	
2006-2007		A/Wisconsin/67/2005	B/Malaysia/2506/2004
2007-2008	A/Solomon Islands/3/2006		B/Florida/4/2006
2008-2009	A/Brisbane/59/2007	A/Brisbane/10/2007	
2009-2010			B/Brisbane/60/2008
2010-2011	A/California/7/2009	A/Perth/16/2009	
2011-2012			
2012-2013		A/Victoria/361/2011	B/Wisconsin/1/2010 (and B/Brisbane/60/2008 for quadrivalent vaccine)
2013-2014			Massachusetts/2/2012 (and B/Brisbane/60/2008 for quadrivalent vaccine)
2014-2015		A/Texas/50/2012	
2015-2016		A/Switzerland/9715293/2013	B/Phuket/3073/2013 (and B/Brisbane/60/2008 for quadrivalent vaccine)
2016-2017		A/Hong Kong/4801/2014	B/Brisbane/60/2008 (and B/Phuket/3073/2013 for quadrivalent vaccine)
2017-2018	A/Michigan/45/2015		
2018-2019		A/Singapore/INFIMH-16-0019/2016	B/Colorado/06/2017(and B/Phuket/3073/2013 for quadrivalnet vaccine)
2019-2020	A/Brisbane/02/2018	A/Kansas/14/2017	
2020-2021	A/Guangdong-Maonan/SWL1536/2019	A/Hong Kong/2671/2019	/Washington/02/2019(and B/Phuket/3073/2013 for quadrivalent vaccine)
2021-2022	A/Victoria/2570/2019	A/Cambodia/e0826360/2020	
2022-2023		A/Darwin/9/2021	/Austria/1359417/2021(and B/Phuket/3073/2013 for quadrivalent vaccine)
2023-2024	A/Victoria/4897/2022		
Total	17 vaccine antigens	30	24

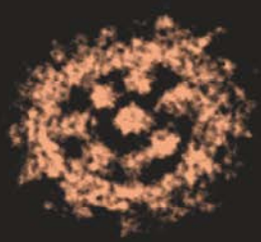

Highly pathogenic avian influenza virus (H5 subtype)


Highly pathogenic avian influenza virus (H5 subtype)
1997····· H5N1


Highly pathogenic avian influenza virus (H5 subtype)
1997 ····· H5N1
2008····· H5Nx
H5N2
H5N6
H5N8


Highly pathogenic avian influenza virus (H5 subtype)
1997 ····· H5N1
2008····· H5Nx
H5N2
H5N6
H5N8
2021 ····· H5N1

Highly pathogenic avian influenza virus (H5 subtype)



1997 ····· H5N1

2008 ····· H5Nx

H5N2

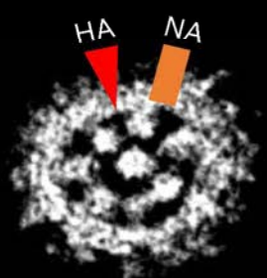
H5N6

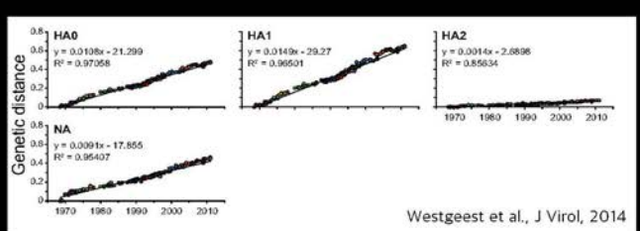
H5N8

2021 ····· H5N1

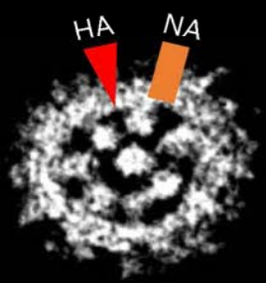
▶ H5 vaccine should be also updated.

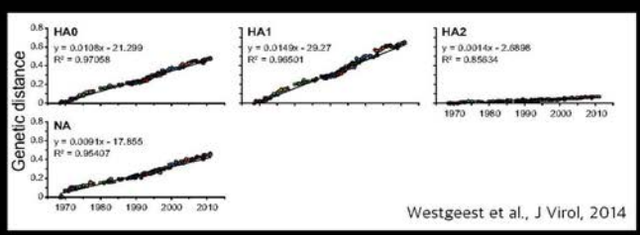
NA mutates less frequently than HA does.





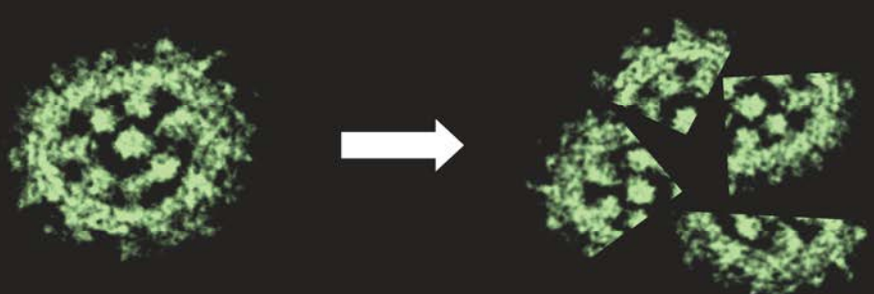
NA mutates less frequently than HA does.





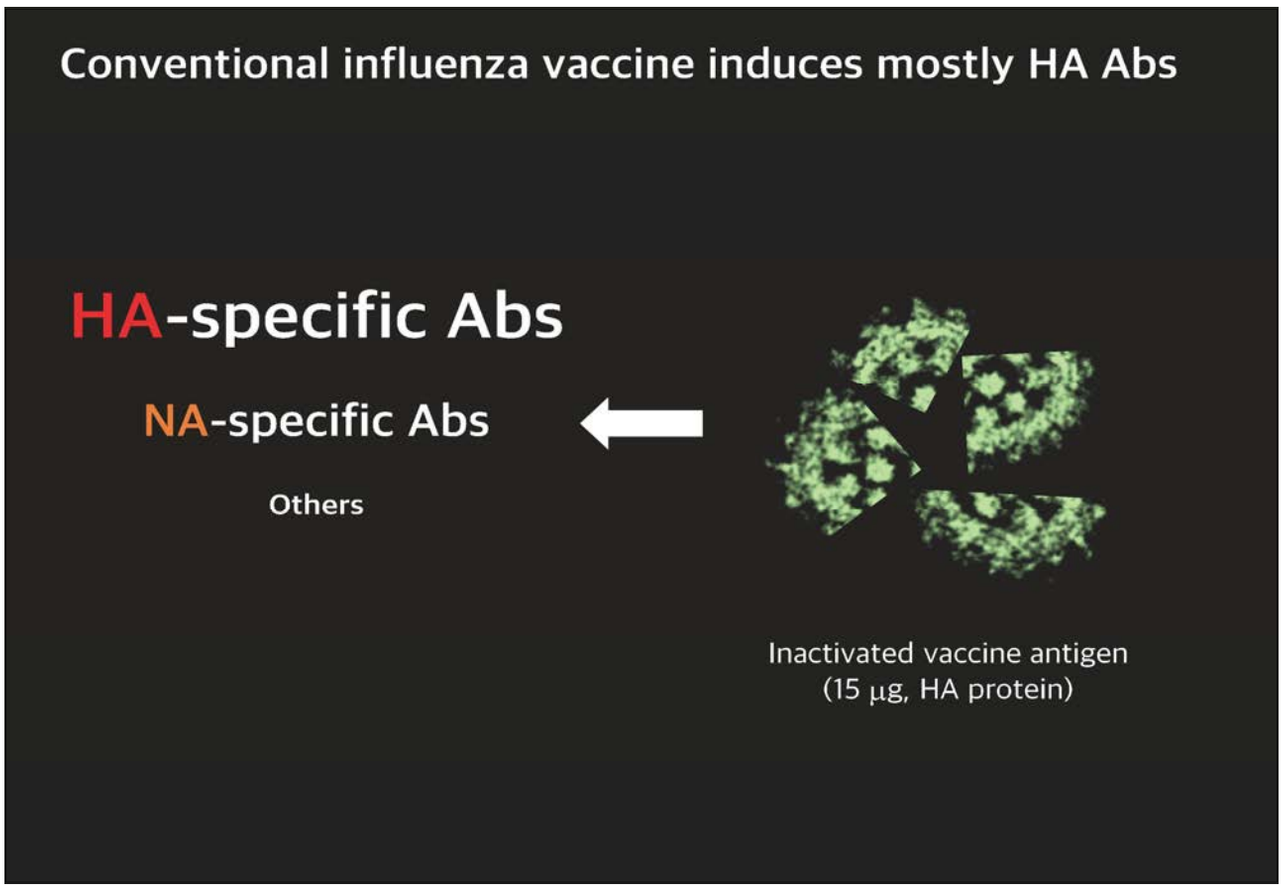
▶ NA exhibits better universal antigen candidacy.

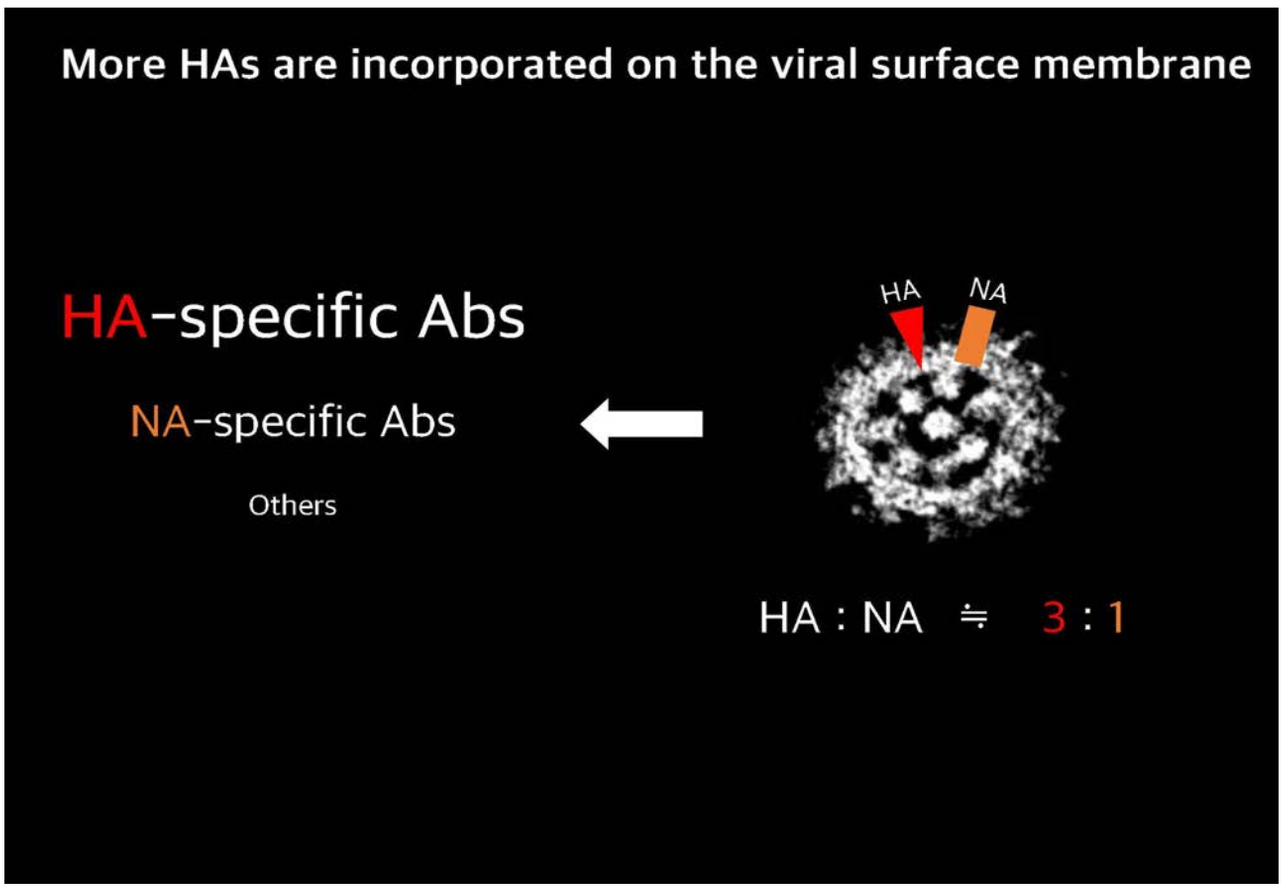
Conventional seasonal influenza vaccine



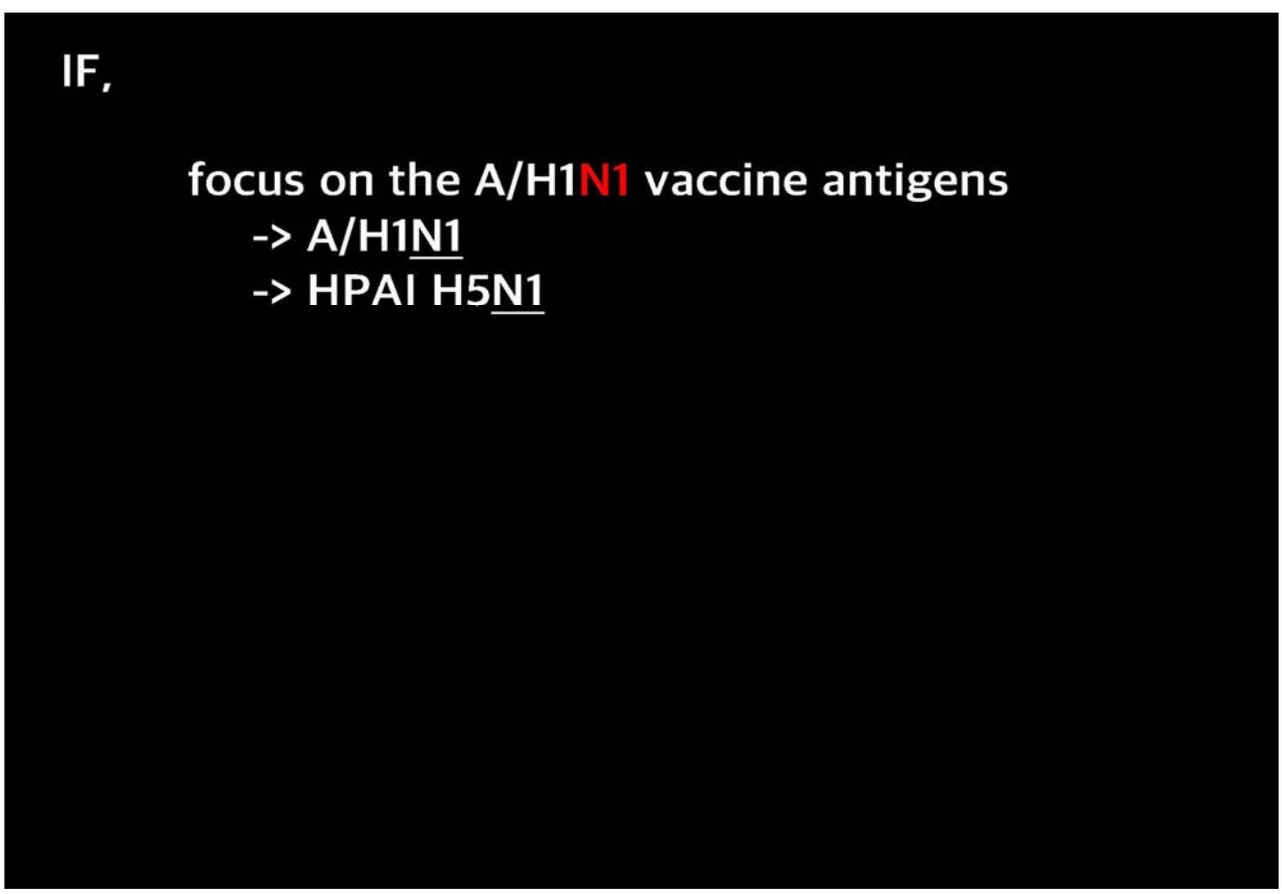
Viral particles

Inactivated vaccine antigen
(15 μg, HA protein)


Conventional influenza vaccine induces mostly HA Abs
HA-specific Abs
NA-specific Abs
Others
Inactivated vaccine antigen
(15 μg, HA protein)


More HAs are incorporated on the viral surface membrane
HA-specific Abs
NA-specific Abs
Others
HA
NA
HA : NA ≒ 3 : 1


IF,


IF,
focus on the A/H1N1 vaccine antigens
-> A/H1N1
-> HPAI H5N1

IF,

focus on the A/H1N1 vaccine antigens
-> A/H1N1
-> HPAI H5N1

focus on the A/H3N2 vaccine antigens
-> various genetic clades of A/H3N2

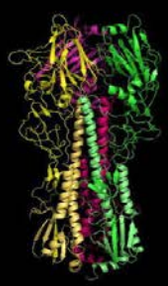
Then, the vaccine candidates may be;

focus on the A/H1N1 vaccine antigens
-> A/H1N1
-> HPAI H5N1
=> inter-subtype universal vaccine

focus on the A/H3N2 vaccine antigens
-> various genetic clades of A/H3N2
=> cross-clade (intra-subtype) vaccine

Each HA and NA vaccine antigen may present;

HA -> Specificity



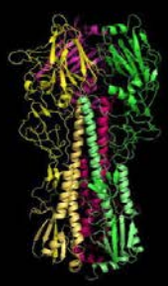
Each HA and NA vaccine antigen may present;

HA -> Specificity

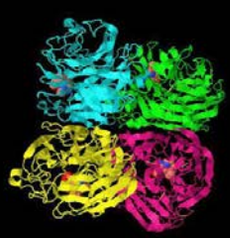
NA -> Universality

Each HA and NA vaccine antigen may present;

HA -> Specificity



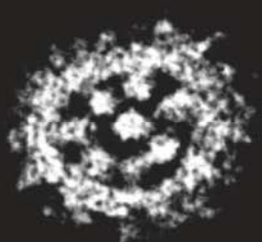
NA -> Universality



The optimized HAS-NAU stategy for better vaccine efficacy

The HAS-NAU strategy;

- protects from seasonal influenza and variants.
- may provide efficacy against HPAI H5N1 viruses.

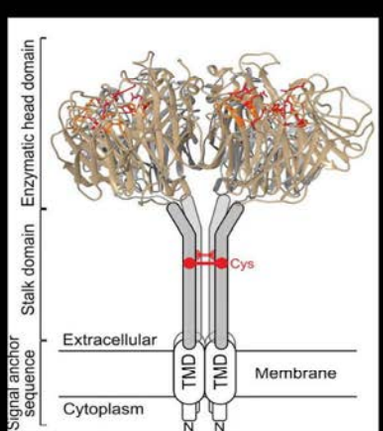


Seasonal influenza virus

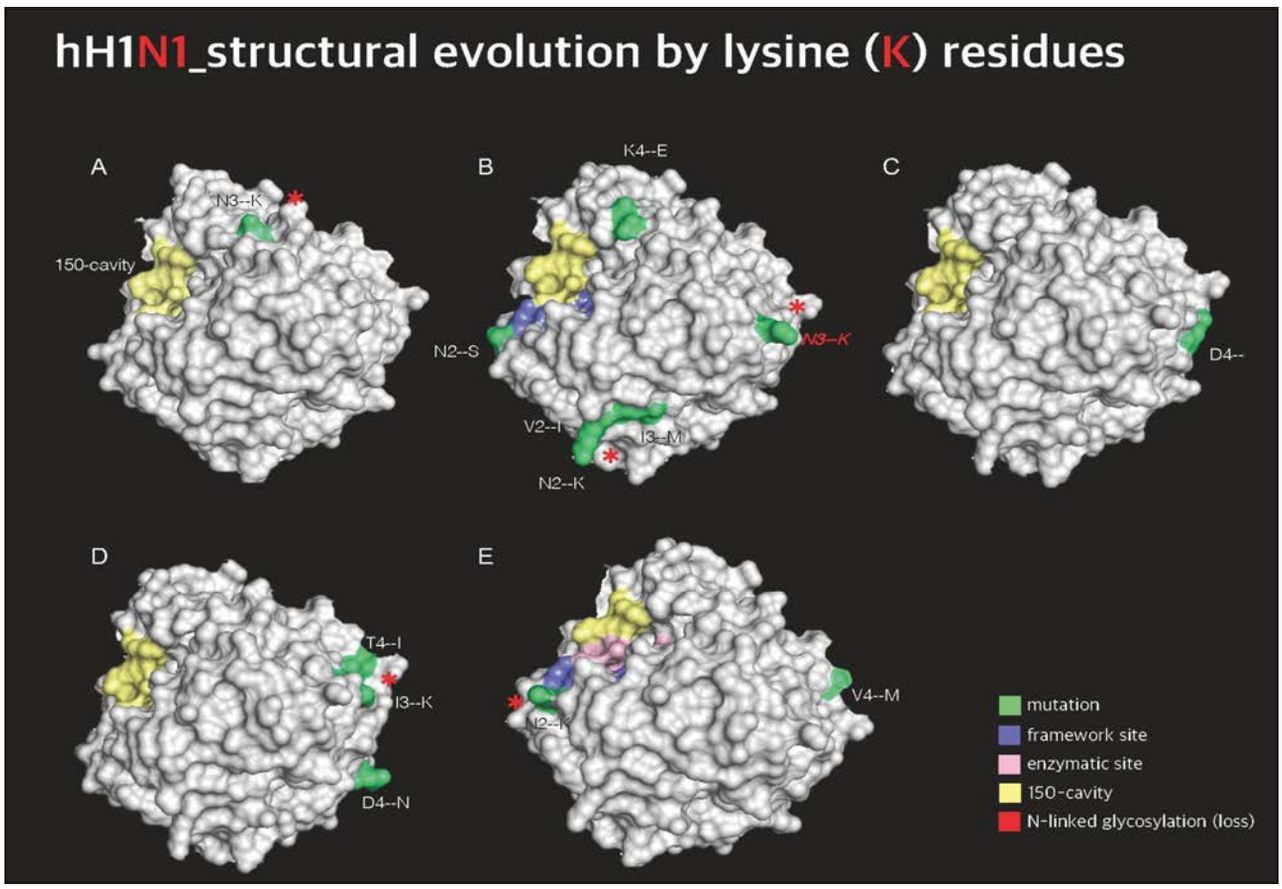
HPAI H5N1 virus

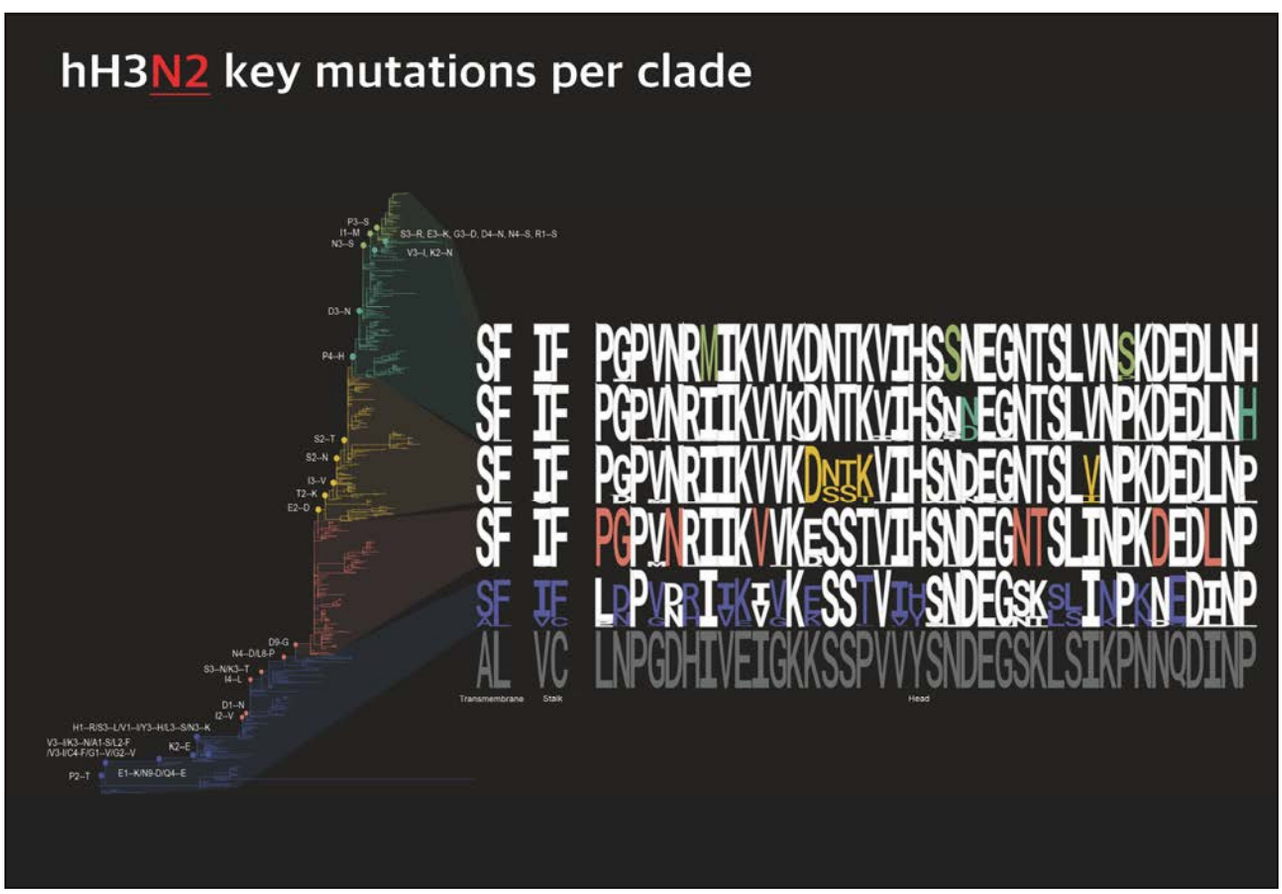
hH1N1 key mutations per clade

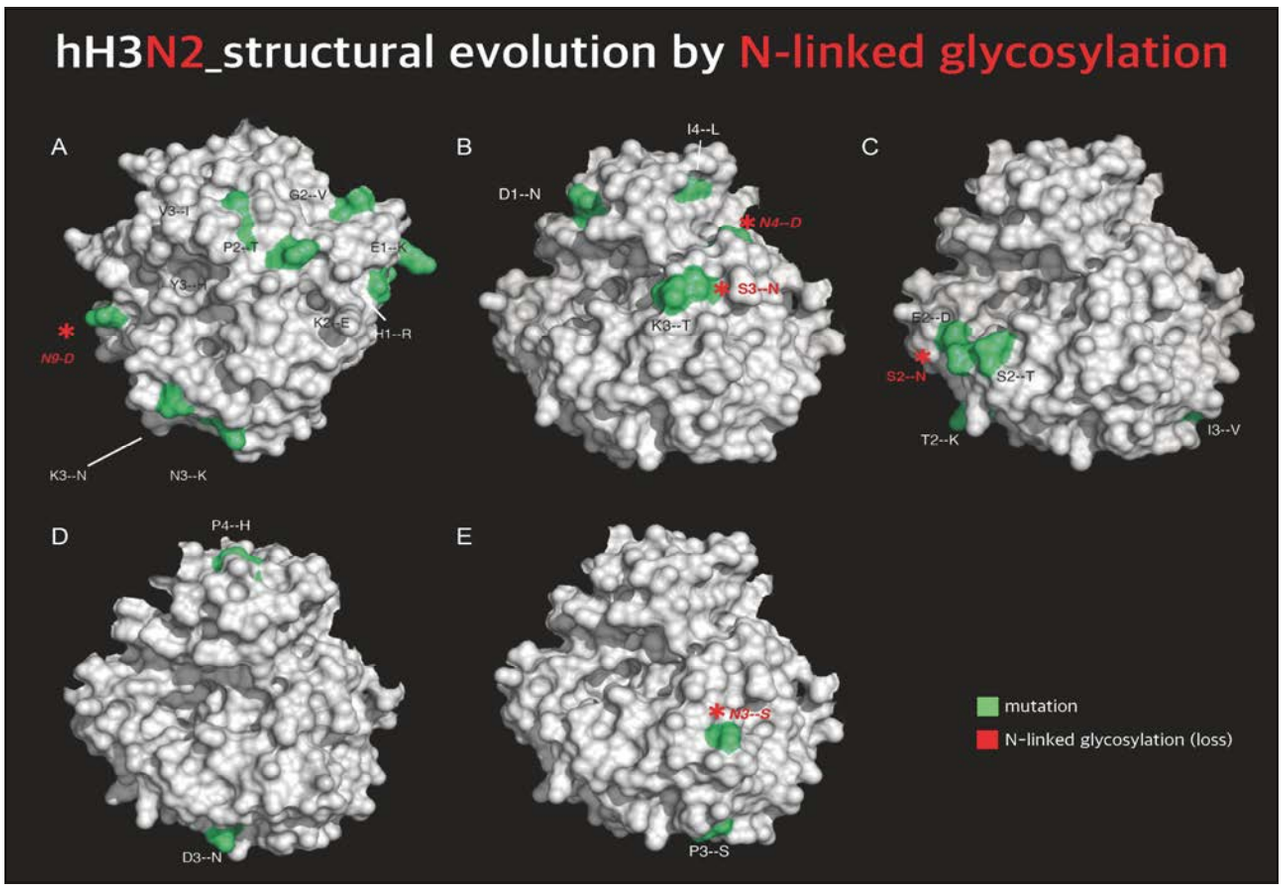
hH1N1 key mutations per clade

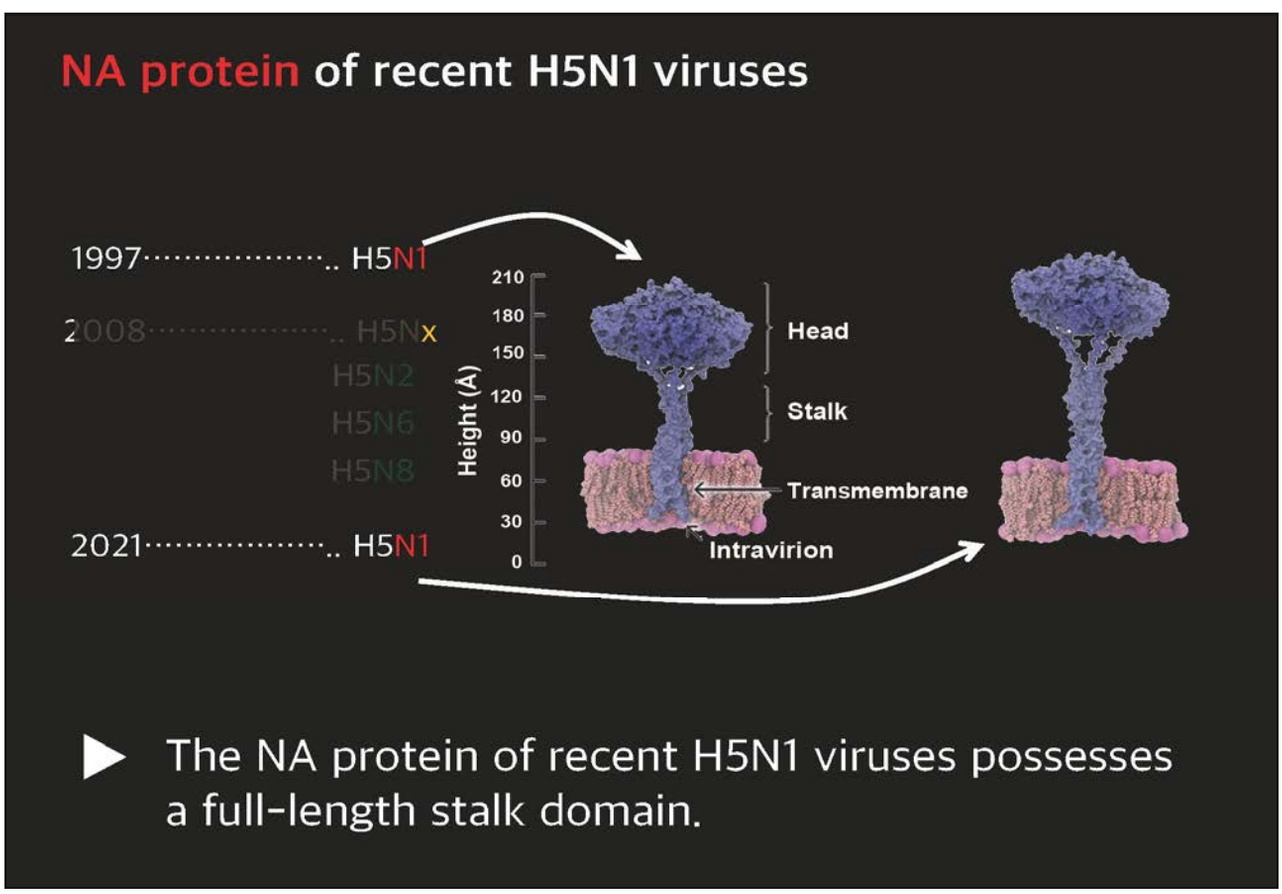


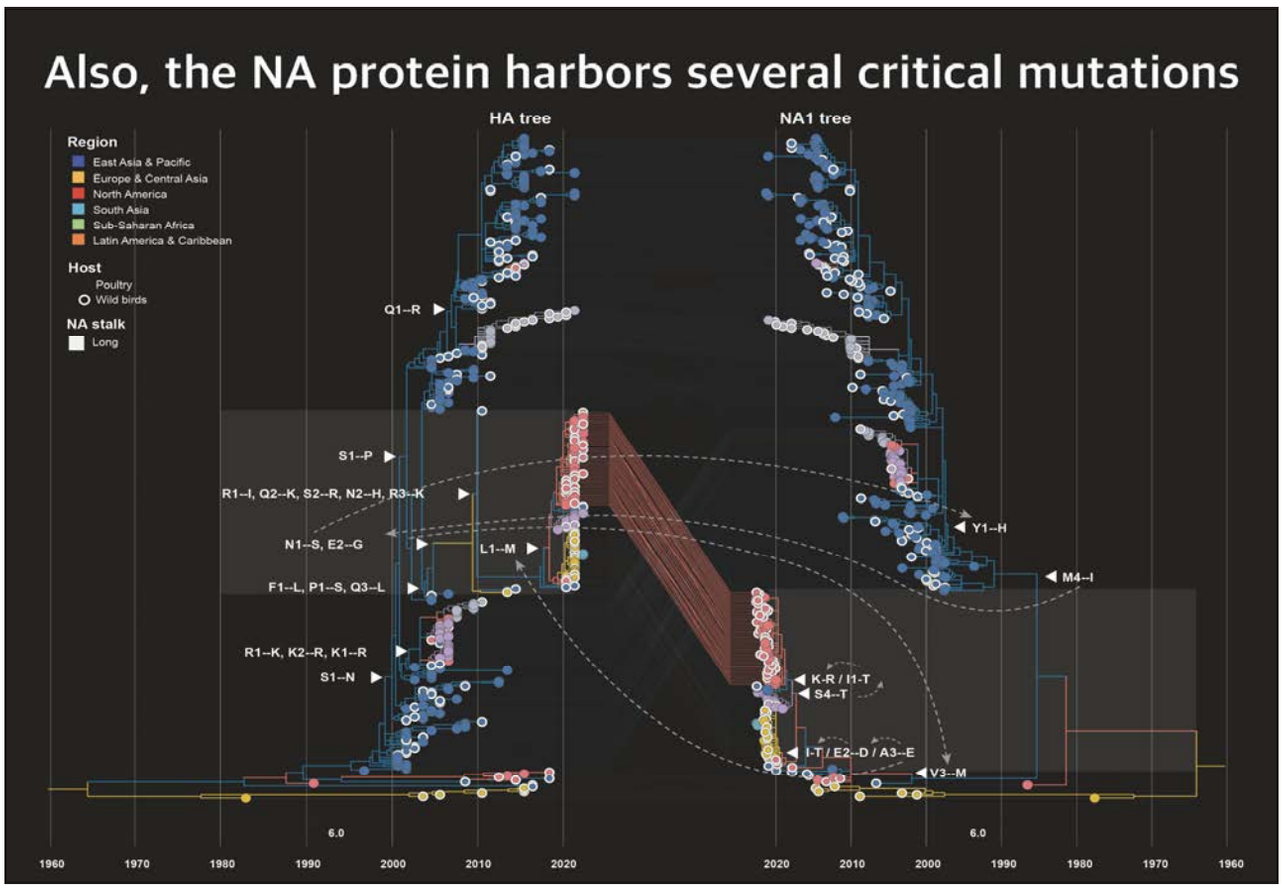
	NA1	NA2
Framework site	E119, R156, W178, S179, D198, I222, E227, H274, E277, N294, E425	
Enzymatic site	R118, D151, R152, R224, E276, R292, R371, Y406	
150-cavity	145-150 (N1 numbering) 147-152 *1149 (N2 numbering)	Lack of 150 cavity V149: salt bridge between D147-H150 (D199 participates)
430-loop	429-437	
Epitope	81, 93, 147, 150-156, 197-199, 218-230, 249-251, 292-300, 328-336, 339-347 367-375, 383-389, 398-405, 428-435	
Ca binding site	• Formed by the oxygen of main chain residue 297, 345, 348 and side chain of N324 Additional a.a. 293, 347, 111-115, 139-143	
Disulfide bond	8 conservative disulfide bond (additional bond in N2, N8, N9) Cys(C)161 of N1	

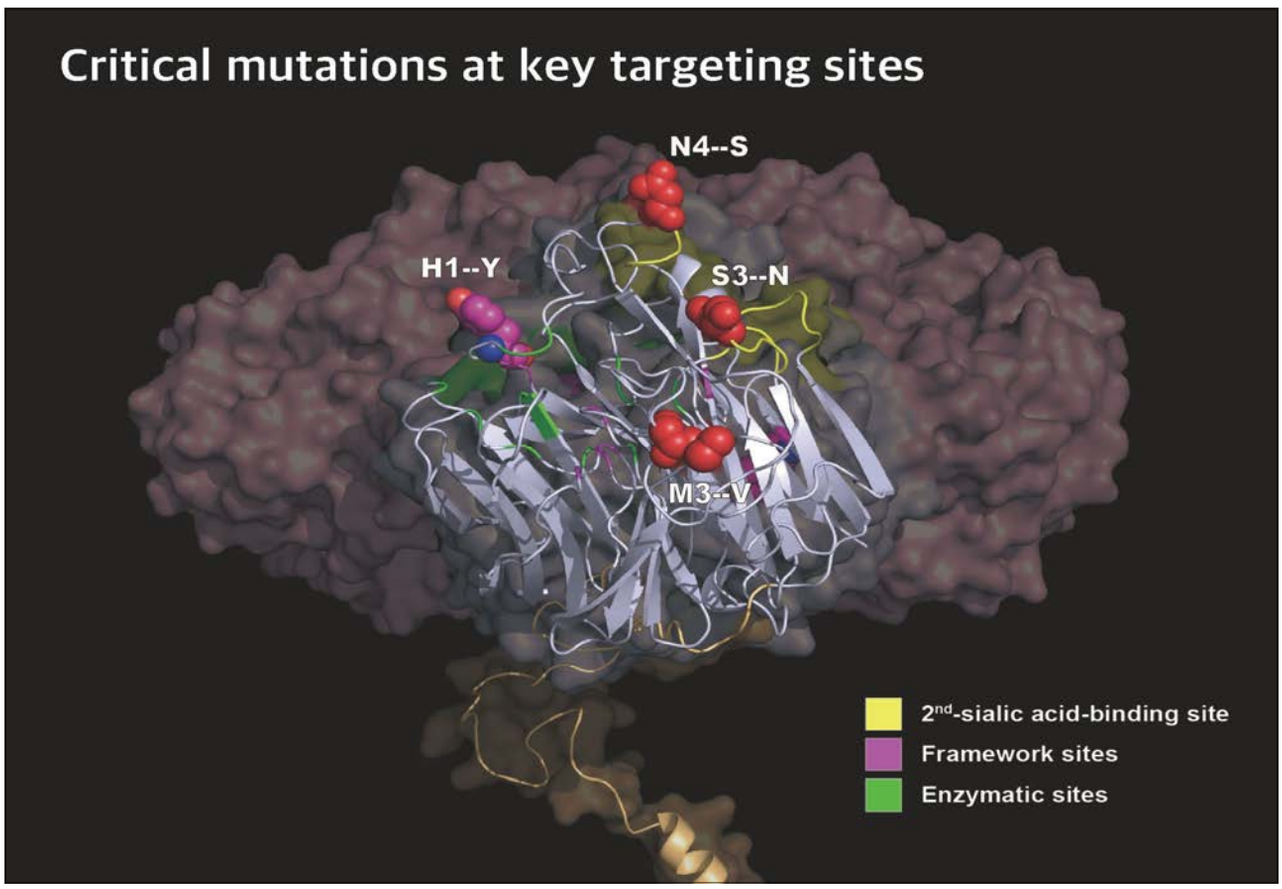

hH1N1_structural evolution by lysine (K) residues
A
N3--K
150-cavity
B
K4--E
N2--S
N3--K
V2--I
I3--M
N2--K
C
D4--
D
T4--I
I3--K
D4--N
E
V4--M
I2--K
mutation
framework site
enzymatic site
150-cavity
N-linked glycosylation (loss)

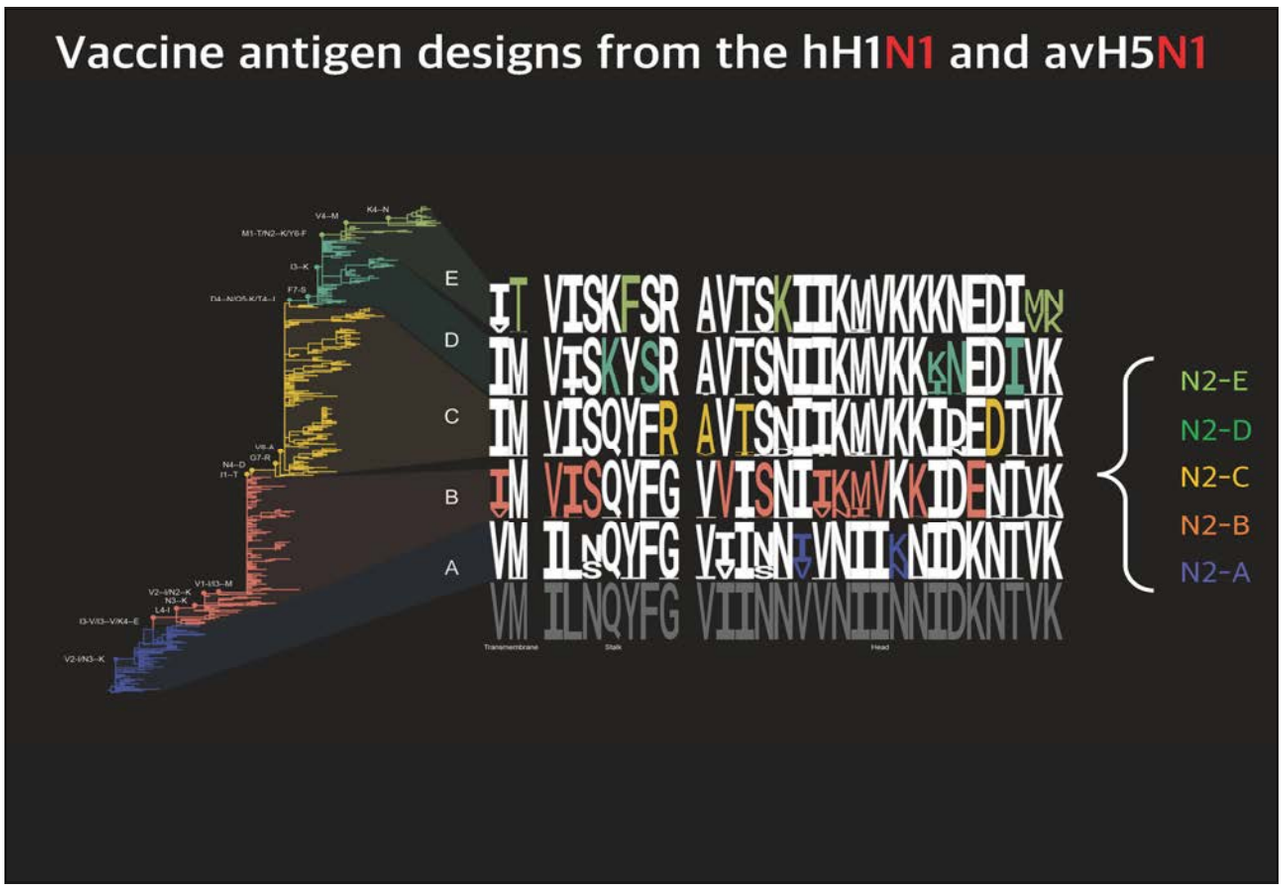

hH3N2 key mutations per clade
P3--S
I1--M
N3--S
S3--R, E3--K, G3--D, D4--N, N4--S, R1--S
V3--I, K2--N
D3--N
P4--H
S2--T
S2--N
I3--V
T2--K
E2--D
D9-G
N4--D/L6-P
S3--N/K3--T
I4--L
D1--N
I2--V
H1--R/S3--L/V1--I/Y3--H/L3--S/N3--K
V3--I/K3--N/A1-S/L2-F
/V3-I/C4-F/G1--V/G2--V
K2--E
P2--T
E1--K/N9-D/Q4--E
Transmembrane
Stalk
Head

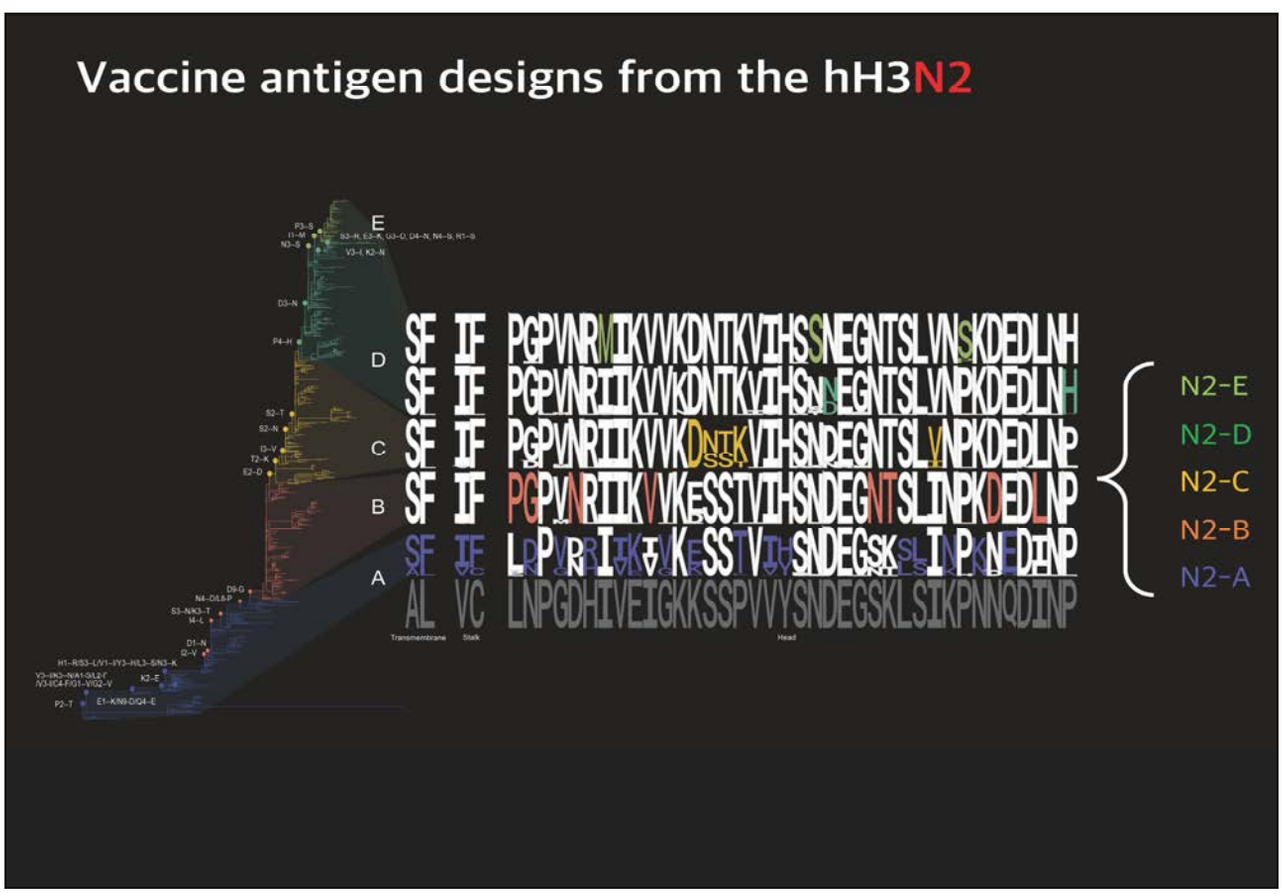

hH3N2_structural evolution by N-linked glycosylation
A
V3--I
G2--V
P2--T
E1--K
Y3--H
K2--E
H1--R
N9-D
K3--N
N3--K
B
I4--L
D1--N
N4--D
S3--N
K3--T
C
F2--D
S2--N
S2--T
T2--K
I3--V
D
P4--H
D3--N
E
N3--S
P3--S
mutation
N-linked glycosylation (loss)


NA protein of recent H5N1 viruses
1997..... H5N1
2008..... H5Nx
H5N2
H5N6
H5N8
2021..... H5N1
Height (Å)
210
180
150
120
90
60
30
0
Head
Stalk
Transmembrane
Intravirion
The NA protein of recent H5N1 viruses possesses a full-length stalk domain.


Also, the NA protein harbors several critical mutations
HA tree
NA1 tree
Region
East Asia & Pacific
Europe & Central Asia
North America
South Asia
Sub-Saharan Africa
Latin America & Caribbean
Host
Poultry
Wild birds
NA stalk
Long
Q1--R
S1--P
R1--I, Q2--K, S2--R, N2--H, R3--K
N1--S, E2--G
L1--M
F1--L, P1--S, Q3--L
R1--K, K2--R, K1--R
S1--N
Y1--H
M4--I
K-R / I1-T
S4--T
I-T / E2--D / A3--E
V3--M
6.0
6.0
1960
1970
1980
1990
2000
2010
2020
2020
2010
2000
1990
1980
1970
1960


Critical mutations at key targeting sites
N4--S
H1--Y
S3--N
M3--V
2nd-sialic acid-binding site
Framework sites
Enzymatic sites

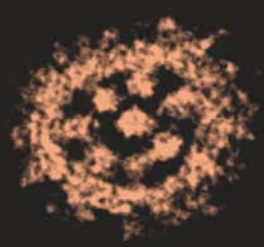

Vaccine antigen designs from the hH1N1 and avH5N1
E
D
C
B
A
N2-E
N2-D
N2-C
N2-B
N2-A
Transmembrane
Stalk
Head


Vaccine antigen designs from the hH3N2
E
D
C
B
A
N2-E
N2-D
N2-C
N2-B
N2-A
Transmembrane
Stalk
Head

The HAS-NAU strategy is set up for the next steps.

- H1, H3 HA vaccine design: WHO recommended HAs
- N1 vaccine designs: to cover hH1N1 and avH5N1
- N2 vaccine designs: to cover various clades of hH3N2

Seasonal influenza virus



HPAI H5N1 virus

Acknowledgement

고려대학교 미생물학교실
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이상이, 박세직, 김현빈, 조승혜, 신우진 대학원생

박만성 교수
김기순 교수
Park's lab 연구진

KU LEUVEN Evolutionary and Computational Virology
Philippe Lemey 교수
Guy Baele 교수
Bram Vrancken 박사


KU MEDICINE
VIC-K
Thank you

03

SFTS mRNA 백신 연구 개발 및 성과

김현국 연구관
국립감염병연구소 감염병백신연구과

Speaker

KIM, Hyeon-Guk

- Korea National Institue of Health
- Senior staff Scientist

EDUCATION:

- 2008 Korea University Graduate School, Ph.D.
- 2002 Korea University Graduate School, Ms.
- 2000 KonKuK university,

PROFESSIONAL EXPERIENCE:

- 2021 ~ presents Senior staff Scientist, Division of infectious disease vaccine research, Korea National Institue of Health
- 2015 ~ 2021 Staff Scientist, Division of Biologics, Ministry of Food and Drug Safety
- 2010 ~ 2015 Staff Scientist, Division of vaccine, Ministry of Food and Drug Safety
- 2009 ~ 2010 Senior researcher, Korea National Institue of Health
- 2008 ~ 2009 Research Professor, Korea unoversity

Topic

SFTS mRNA Vaccine Research and Development

Abstract

Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne emerging infectious disease and caused by Dabie bandavirus also known as SFTS virus (SFTSV) belonging to the genus Bandavirus. Since SFTS first reported in China in 2012, subsequently confirmed cases in recent years have been reported in South Korea and Japan with high mortality rate of over 20%. Despite the wide distribution and high fatality of SFTS, there is no licensed vaccine. Therefore, we evaluated immunogenicity and protective efficacy of SFTSV mRNA vaccine with research collaboration of Korea NIH and Moderna in mice.

As a result of our study, the selected candidates showed more humoral and cellular immune responses as well as stimulating protective immunity than others. It indicated that these candidates have possibility as the most promising candidates for protection against SFTSV infections

04

Sarbecoviruses에 대한 단일클론항체 및 범용 백신연구개발 및 성과

Wang Linfa Professor

DUKE-NUS, Singapore Executive Director for the Programme for Research in Epidemic Preparedness and Response

Speaker

Wang Linfa

- Professor in the Programme in Emerging Infectious Diseases at DUKE-NUS Medical School, Singapore
- Executive Director for the Programme for Research in Epidemic Preparedness and Response (PREPARE), Singapore
- Professor

EDUCATION:

- 1986 Ph.D. Biochemistry (Molecular Biology), University of California, Davis.
- 1982 B.S. (Honour) Biology (Biochemistry), East China Normal University, Shanghai, China

PROFESSIONAL EXPERIENCE:

- 2021 ~ Present Director, BMGF Asia Pathogen Genomics Initiative (PGI) Center
- 2021 ~ Present Executive Director, PREPARE (Programme for Research in Epidemic Preparedness and Responses), Singapore
- 2020 ~ Present Professor, Program in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore
- 2012 ~ 2020 Director and Professor, Program in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore
- 2008 ~ 2015 OCE Science Leader, CSIRO Australian Animal Health Laboratory, Geelong, Vic.

Topic

Broad spectrum vaccine and mAbs for sarbecoviruses

Abstract

Although the public health emergency is over for the COVID-19 pandemic, the virus variants are continuously circulating and mutating. It is therefore necessary for us to continue our effort to develop better and more effective vaccines and other countermeasures. In this presentation, we will focus on our approach for cross-clade boosting vaccine development as well as our latest data on broad-spectrum neutralizing human monoclonal antibodies for SARS-CoV-2, SARS-CoV-1 and animal sarbecoviruses.

세션 4.

신종감염병 백신개발 현황 및 전략

2024
감염병연구기관 국제심포지엄
International Symposium for Infectious Diseases Research Institutes Cooperation

Chair

Kevin Kee-Jong Hong

- Gachon Univ. School of Medicine
- Professor, Gachon Univ. School of Medicine & Director General, Korea mRNA Vaccine initiative (KmVAC)

EDUCATION:

- 2001 Texas Tech University, TX, U.S.A.(Ph.D.)
- 1991 Seoul National University, Seoul.(M.S.)
- 1988 Seoul National University, Seoul, Korea.(B.S.)

PROFESSIONAL EXPERIENCE:

- 2022 ~ Present Professor, Research related to vaccine development, Gachon Univ. School of Medicine, Inchon, Korea
- 2022 ~ Present Director General, Korea mRNA Vaccine initiative (KmVAC), Seongnam, Korea
- 2023 ~ Present Member, Selection Committee, RIGHT Foundation, Seoul, Korea
- 2020 ~ 2022 Professor, General R&D planning for establishment of the infectious disease graduate school of KU-KIST program, Konkuk Univ., Seoul, Korea
- 2017 ~ 2019 Executive Director, Launching newly opened industrial R&D center, Interpark Bio-Convergence, Seoul, Korea
- 2016 ~ 2017 Scientific Consultant for the Director General, Vaccine preparedness strategy, International Vaccine Institute, Seoul, Korea
- 2014 ~ 2015 Executive Director, R&D Planning & Business Development, Institut Pasteur Korea, Seongnam, Korea
- 2012 ~ 2014 Director, Molecular imaging development for vaccine development, nano-medicine and convergent technology group, Korea National Institute of Health, Osong, Korea

PROFESSIONAL EXPERIENCE:

- 2013 ~ 2014 Governmental Representative, “Able Response (Korea-U.S.A. annual joint planning practice for the biothreat preparedness)”, Ministry of Health and Welfare, Sejong, Korea
- 2011 ~ 2014 Deputy Director, Dept. high-risk pathogen research, Anthrax and Tularemia Vaccine development, Korea Center for Disease Control and Prevention, Osong, Korea
- 2011 ~ 2012 Deputy Director, Taskforce for institutional vaccine research (VRC planning team), Korea National Institute of Health, Osong, Korea
- 2009 ~ 2011 Deputy Director, Dept. of Influenza viruses, Universal Vaccine development, Korea National Institute of Health, Seoul, Korea
- 2007 ~ 2009 Senior Scientist, Dept, of AIDS and oncological viruses, AIDS therapeutics development, Korea National Institute of Health, Seoul, Korea
- 2004 ~ 2006 Research Associate, Dept. of Microbiology, AIDS and Tularemia pathogenesis, Univ. of Kansas Medical Center, Kansas City, Kansas, U.S.A.
- 2003 ~ 2004 Research Associate, Clinical Oncology Lab, Southwest Cancer and Research Center, Lubbock, TX, U.S.A.
- 2002 ~ 2004 Postdoc, Dept of Pathology, Texas Tech Health Sci. Center, Lubbock, TX, U.S.A.

01

백신 면역증강기술

염정선 대표
차백신연구소

Speaker

Jung-Sun Yum

- CHA Vaccine Institute
- CEO

EDUCATION:

- 1992 Syracuse University, Ph.D.
- 1985 Seoul National University, BS

PROFESSIONAL EXPERIENCE:

- 2014 ~ present CEO, CHA Vaccine Institute
- 2011 ~ 2014 Head of R&D center, CHA Vaccine Institute
- 2000 ~ 2011 Director, Dobeel Corp.
- 1993 ~ 2000 Principal investigator, Mogam Biotechnology Research Institute

Topic

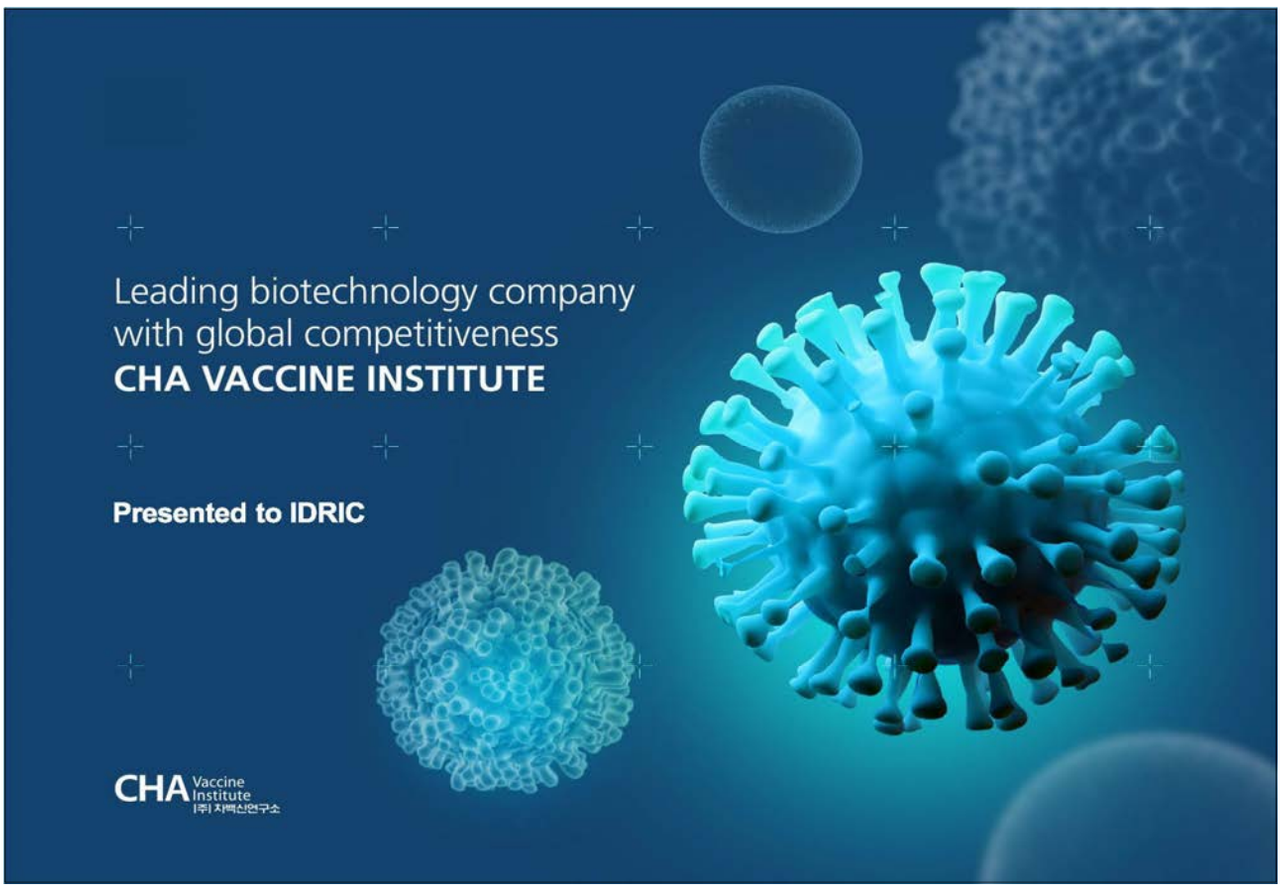
Vaccine adjuvant platform

Abstract

CHA Vaccine Institute is a “clinical stage biotech company” focused on the vaccines, both prophylactic and therapeutic for infectious disease, as well as cancer immunotherapy.

Our core technology is vaccine adjuvant platform, which is based on TLR2 and TLR3 agonists. Vaccine adjuvant is a substance that increases or modulates the immune response to a vaccine. By using adjuvant technology, we can improve the efficacy of the current vaccines and also develop novel vaccines.

In this presentation, I will introduce functional advantages of our adjuvant L-pampo and Lipo-pam and explain the current status of our vaccine pipelines using this platform.



Executive Summary

CHA Vaccine Institute (KOSDAQ: 261780) is a dynamic biotechnology company that specializes in the development of groundbreaking therapeutic and prophylactic vaccines, along with innovative cancer immunotherapies.

Key Points

- **Cutting-Edge Adjuvant Platforms:** Our TLR2/TLR3 agonist combination significantly improves vaccine and anti-cancer efficacy.
- **Tackling Urgent Medical Needs:** We address critical medical needs, including Chronic Hepatitis B ($5.6 billion) and Herpes Zoster ($5.0 billion).
- **Advancing Clinical Trials:** We have three ongoing trials, including a Phase 2b vaccine and two Phase 1 prophylactic vaccines.
- **Strong Intellectual Property:** With 40 worldwide patents, we ensure robust protection for our innovative solutions.
- **Experienced Leadership:** Our team provides expert guidance in the biotech field.
- **Seeking Partnerships:** We actively seek partnerships to co-develop and out-license our revolutionary adjuvant platforms, vaccines, and cancer immunotherapies. Join us in revolutionizing healthcare and making a lasting global impact.

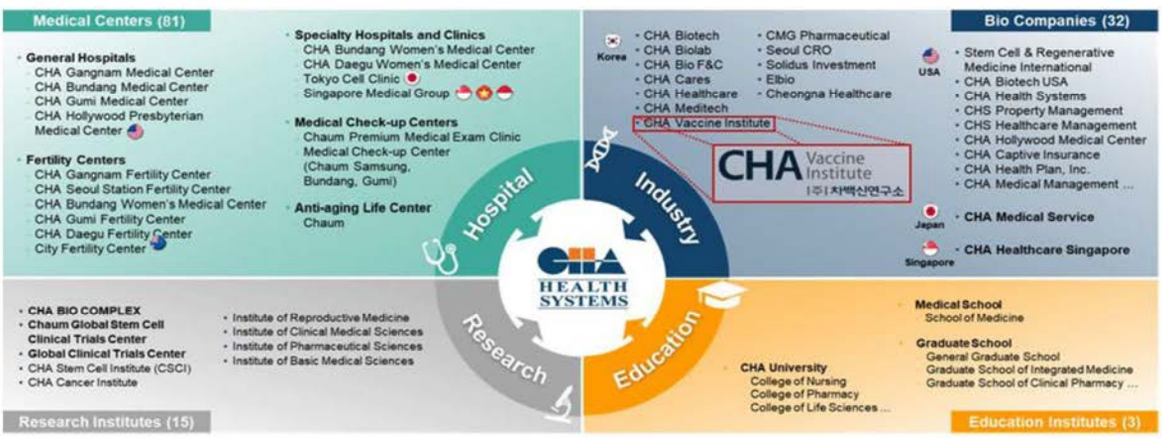
Prologue. CHA Health Systems: Industry – Academy – Research – Hospital

CHA Vaccine Institute 주식회사 차백신연구소

Hospital
- 81 Medical Centers across 7 Countries (15 in Korea & 66 overseas)
- 1,730 HCPs and 14,000 Employees

Research
- 7 Reproductive Medicine Research Centers with over 150 Researchers
- CHA Advanced Research Institute with 10 Labs and 31 Researchers

※ Q1 2022



Prologue. Our Corporate Identity

CHA Vaccine Institute 주식회사 차백신연구소

Specialized in next generation vaccines and immunotherapies, based on proprietary adjuvant platform technology

Unique TLR 2/3-based Adjuvant Platforms

- Development of novel vaccines & therapeutic vaccines
- Development of cancer immunotherapy & cancer vaccines

Development of novel and competitive vaccines & immunotherapies

Addressing target markets with large market size and unmet medical needs

Hepatitis B(HBV)	Herpes Zoster	Influenza / COVID-19	Cancer Immunotherapy	Cancer Vaccines
First-in-Class chronic hepatitis B therapeutic vaccine / Best-in-Class vaccine for non-responders	First-in-class therapeutic HZ vaccine / Best-in-Class prophylactic HZ vaccine	Vaccines for outbreaks	Immune checkpoint inhibitor combination by heating up the cold tumor	Combination therapy / Prevention of recurrence
Approx. U$ 5.6 Bil. (Global market size)	Approx. U$ 3.0 Bil. (Global market size)	Approx. U$ tens of Bil. (Global market size)	Approx. U$ 85 Bil. (Global market size)	Approx. U$ 4.0 Bil. (Global market size)

Our Product Pipeline

CHA Vaccine Institute 지제약연구소

Specialized in proprietary adjuvant-based vaccines and immunotherapies, for the treatment of infectious diseases, chronic diseases, and cancers

Program	Pipeline	Development Phase
Infectious Disease	Chronic Hepatitis B Therapeutic Vaccine (CVI-HBV-002)	Discovery → Preclinical → Phase 1/2a → Phase 2b
	Prophylactic HBV Vaccine (CVI-HBV-002)	Discovery → Preclinical → Phase 1
	Herpes Zoster Vaccine (CVI-VZV-001)	Discovery → Preclinical → Phase 1
	Sublingual COVID-19 Vaccine (CVI-SL-CoV-001)	Discovery; Collaboration with BIOLINGUS
	Flu-COVID-19 Combined Vaccine (CVI-FluCOVID-001)	Discovery
Cancer	Cancer Immunotherapy (CVI-CT-001)	Discovery → Preclinical
	Multi-peptide Cancer Vaccine (CVI-CV-001)	Discovery
	HSP-90 epitope peptide Cancer Vaccine (AST-021p Aston Sci.)	Discovery → Preclinical; Collaboration with Aston sci.

CVI's Adjuvant Platforms Offer Advantages Over Conventional Adjuvants

CHA Vaccine Institute 지제약연구소

- **L-pampo™ & Lipo-pam™: Innovative adjuvant platforms utilizing TLR2 and TLR3 agonists that demonstrate excellent synergistic effects in inducing robust humoral & cellular immune responses**
  - Superior performance in diverse vaccines targeting infectious diseases and cancers
  - Proven clinical safety for over 200 patients (up to phase 2b)
  - Diverse formulations capable of delivering peptides, proteins, and nucleic acids as antigens
  - Not derived from natural products; a combination of synthesized materials
  - Scalable manufacturing process
  - Long-term stability in liquid vaccine formulation: 36 months at 2~8°C

Superior performance, Safety, Stability

Innovative TLR-based Adjuvant Platforms: L-pampo™ & Lipo-pam™ (1)

CHA Vaccine Institute 지제약연구소

L-pampo™ & Lipo-pam™ are innovative adjuvant platforms that utilize TLR2 and TLR3 agonists to demonstrate excellent synergistic effects in inducing robust T cell activation

	1st Generation	2nd Generation	3rd Generation
Components	Alum	Non-TLR	LPS, lipopeptide peptidoglycan, flagellin, TLR4, TLR2, TLR1, TLR5, TLR7, TLR9, TLR3, ssRNA, unmethylated CpG DNA, dsRNA, cell membrane, endosomal membrane
Major immune effects	• Acts as antigen delivery vehicle - slowly releases antigen and results in prolonged immune response		Harnesses innate immunity to promote adaptive immunity
Adjuvants	• Aluminum salts	• MF59 • AS03 • Emulsion, liposome	Unique adjuvant platforms with TLR 2/3 agonists, L-pampo™ & Lipo-pam™
			Therapeutic vaccine for chronic hepatitis B / Prophylactic vaccine for HBV / Prophylactic vaccine for Herpes Zoster

Innovative TLR-based Adjuvant Platforms: L-pampo™ & Lipo-pam™ (2)

CHA Vaccine Institute 지제약연구소

Scalable platforms from infectious diseases, to chronic diseases, to oncology

L-pampo™

Complex of TLR2 & TLR3 agonists

TLR2 agonist (cell memb.)
+
TLR3 agonist (endosomal memb.)

- **Excellent immune-boosting effect of L-pampo™**
  - 100x higher antibody induction than Alum
  - Excellent adjuvanticity over MPL, CpG, and MF59
  - Inducing mucosal immunity
  - → **Robust T cell activation and antibody induction**
- **Clinical safety proven: phase 2b ongoing**
- **Vaccine pipeline using L-pampo™:** Chronic hepatitis B therapeutic vaccine, Prophylactic HBV vaccine for non-responders, COVID-19 vaccine, Cancer vaccines

Lipo-pam™

Liposomal formulation of L-pampo™

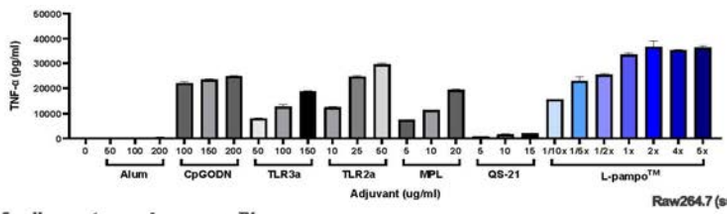
Liposome → CVI-ADJ-005 (Cationic liposome, TLR2 ligand) → CVI-ADJ-006 (CVI-ADJ-005, TLR3 ligand)

- **Complex of TLR2 and/or TLR3 agonists formulated in liposomes**
  - Dual effect: Immune response booster + Ag delivery vehicle
  - Applicable to peptide, protein, DNA and RNA vaccines
- **Designed to induce stronger cell-mediated immunity**
- **Inducing mucosal immunity**
- **Vaccine pipeline using Lipo-pam™:** Herpes Zoster vaccine, Norovirus vaccine, Cancer vaccines

L-pampo™ Induces Higher Production of Pro-inflammatory Cytokines (*in vitro*)

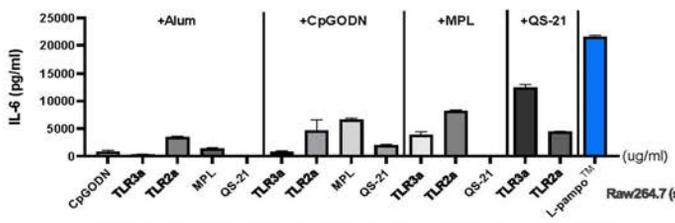
CHA Vaccine Institute 차백신연구소

Single adjuvants vs. L-pampo™



Raw264.7 (subject: mouse)_24 h_TNF-α_ELISA

Combination of adjuvants vs. L-pampo™



Raw264.7 (subject: mouse)_24 h_mIL-6_ELISA

L-pampo™ exhibits a superior capability for inducing pro-inflammatory cytokines compared to conventional TLR-based adjuvants such as TLR2, TLR3, TLR4, TLR9 agonists, as well as Alum and QS-21, whether used alone and in combination.

L-pampo™ & Lipo-pam™ Enhance Cellular & Humoral Immunity (*in vivo*)

CHA Vaccine Institute 차백신연구소

Target vaccines	Head-to-head comparisons	Animal strains	Summary
HBV vaccine	• Alum • AddaVax™ • CpG ODN (TLR9 agonist)	• C57BL/6 mice • BALB/c mice • HBsAg/HLA-A2 Tg mice	L-pampo™ induces the strongest humoral and cellular immune responses.
Influenza vaccine	• Alum • AddaVax™	• BALB/c mice (Young, Aged)	L-pampo™ induces superior protection efficacies in terms of HI titers and IgG GMT, and the highest cell-mediated immunity.
H7N9 avian influenza Vaccine	• Alum • AddaVax™	• BALB/c mice • Ferret	L-pampo™ induces superior protection efficacies in terms of HI titers, IgG GMT, and lung virus titers, as well as the highest cell-mediated immunity.
SARS-CoV-2 vaccine	• Alum • AddaVax™ • AddaS03™ (AS03-like) • CpG	• Ferret • BALB/c mice	L-pampo™ induces the highest neutralizing antibody titers and strongest cell-mediated immunity.
Peptide cancer vaccine (breast cancer)	• Incomplete Freund's Adjuvant (IFA) & Complete Freund's Adjuvant (CFA) • TLR4 agonist (MPL)	• C57BL/6 mice • FVB/N-Tg (MMTVneu) mice	L-pampo™ induces the strongest Th1 immune response.
Japanese encephalitis vaccine	• Alum • Alum+TLR4 agonist (AS04-like)	• BALB/c mice	L-pampo™ induces the highest antigen-specific antibody production and cell-mediated immunity.
Acellular pertussis vaccine	• *M. Tuberculosis* derived TLR4 agonist • Cholera toxin-based adjuvant • Alum	• BALB/c mice	L-pampo™ induces the strongest humoral immune response and enhances the production of class-switched IgG antibodies.
HIV vaccine	• Alum • IFA	• BALB/c mice	L-pampo™ induces the highest humoral immune response.
Herpes Zoster vaccine	• AS01: liposome+MPL+QS-21 • AS02: MF59+MPL+QS-21 • QS-21 only	• C57BL/6 mice	Lipo-pam™ induces the most effective humoral and cellular immune responses.
Mucosal vaccine (OVA – model Ag)	• Alum	• BALB/c mice	L-pampo™ induces the most potent mucosal, humoral, and cellular immune responses.
Norovirus vaccine	• Alum • Alum+TLR4 agonist (AS04-like) • Cholera toxin-based adjuvant	• BALB/c mice	L-pampo™ & Lipo-pam™ induce the most effective humoral (IgG Ab, IgA Ab, HBGA Blocking Ab) and cellular immune responses.

Innovative TLR-based Adjuvant Platforms: L-pampo™ & Lipo-pam™ (3)

CHA Vaccine Institute 의학 지제약연구소

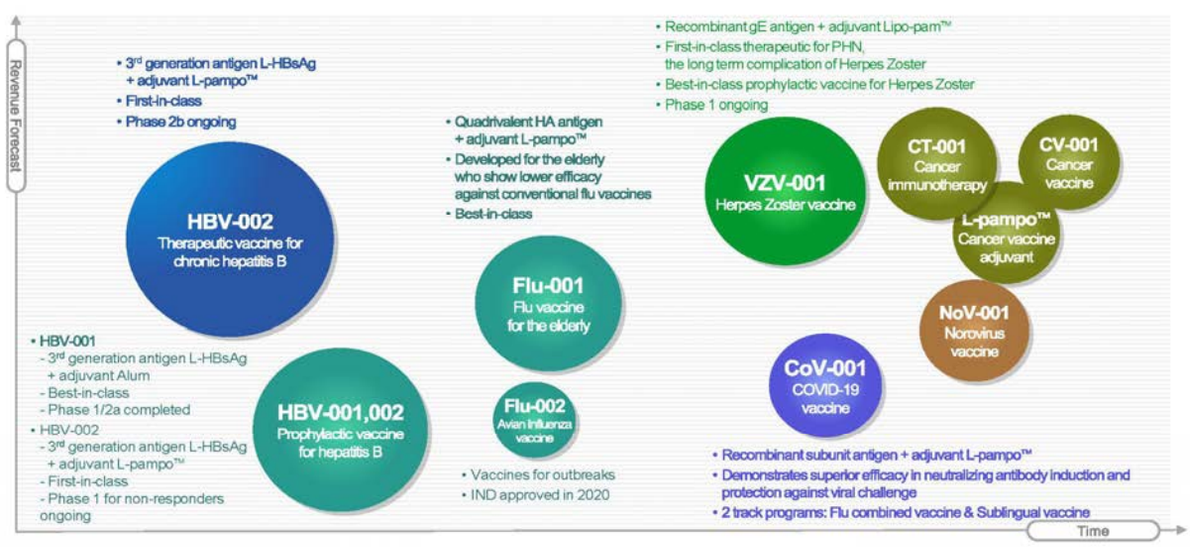
Effective & Versatile Adjuvants for Vaccine Development

Breaking immune tolerance with a strong immune response	• Chronic hepatitis B therapeutic vaccine
Enhancing cell-mediated immune response (Th1)	• Chronic hepatitis B therapeutic vaccine • Recombinant Herpes Zoster vaccine
Therapeutic T cell vaccine	• Cancer Immunotherapy • Anti-cancer vaccine
Boosting immune response in the elderly	• Influenza vaccine
Inducing long-lasting immune response	• Influenza vaccine
Sparing antigen dose	• Influenza vaccine
Inducing mucosal immunity	• Norovirus vaccine • Sublingual COVID-19 vaccine

Portfolio Scalability Using CVI's Adjuvants

CHA Vaccine Institute 의학 지제약연구소

With its unique and competitive adjuvant platforms,
CVI will build a strategic portfolio and generate a solid revenue

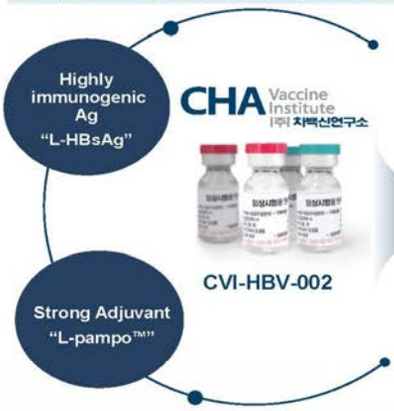


CVI-HBV-002: adjuvanted HBV vaccine, very potent vaccine

CHA Vaccine Institute 주식회사 차백신연구소

Therapeutic potential was confirmed using HBsAg/HLA-A2 Tg mouse model
To overcome immune tolerance and eradicate HBV antigens*

- 3rd generation antigen including preS and S Ag
- Highly immunogenic
- Glycosylated VLP (Virus Like Particle) Ag



Strong immune responses both humoral & CMI

Therapeutic vaccine for chronic hepatitis B
- Phase 2b on-going

- Overcome immune tolerance
- Th1 response
- Functional cure

Prophylactic vaccine for non-responders
- Phase 1 on-going

- Rapid protection
- High Ab titers

- Complex of TLR2 & TLR3 agonists
- Synergistic effects in inducing immune responses (both humoral & cellular)
- Th1 immune response induced

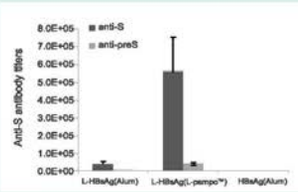
*published in Clinical Vaccine and Immunology in 2012

CVI-HBV-002: Therapeutic Potential in HBsAg/HLA-A2 Tg Mouse Model*

CHA Vaccine Institute 주식회사 차백신연구소

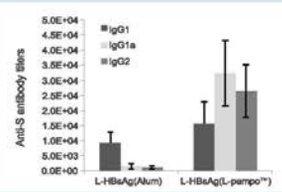
CVI-HBV-002 enhances immune responses & reduces blood HBsAg
in the immune-tolerant model

Ab titers: anti-S, anti-preS



- Highest Ab titers in the L-HBsAg + L-pampo™ group (CVI-HBV-002)
- No Ab response in the HBsAg + Alum group (conventional 2nd gen. HBV vaccine)

Ab isotypes



- Ab isotype switching observed in the L-HBsAg + L-pampo™ group (CVI-HBV-002)

→ Inducing strong Th1 response

HBsAg reduction in the blood

HBV vaccine	Antigen +Adjuvant	Decrease rate of HBsAg	# of cured mouse (%)
CVI	L-HBsAg + Alum	58.8 %	1/7(14.29)
	L-HBsAg + L-pampo™	81.9%	5/7(71.43)
2nd Gen.	HBsAg + Alum	12.2%	0/7(0.00)

- HBsAg reduced in the L-HBsAg + L-pampo™ group (CVI-HBV-002)

→ Complete disappearance of HBsAg in 5/7 mice (71%)

Proved the potential to achieve functional cure
by overcoming immune tolerance and inducing immune response in CHB patients

* A model for T cell tolerance to hepatitis B surface antigen in chronic hepatitis B virus infection developed by Institut Pasteur

CVI-VZV-001: Recombinant Herpes Zoster Vaccine in Phase 1

CHA Vaccine Institute 주식회사 지에스신약연구소

Preclinical studies of CVI-VZV-001 have demonstrated tolerability and higher immunogenicity.

Advantages

- Inducing strong CMI
- First- in-Class (Therapeutic)
- Best-in-Class (Prophylactic)

CVI-VZV-001 with improved immunogenicity, safety & productivity

- Liposome formulation with adjuvant L-pampo™
- Dual acting (Ag delivery & Immune booster)
- Robust CMI response
- Safety proven by CVI adjuvanted vaccine studies

Excellent adjuvant "Lipo-pam™"

Recombinant antigen "gE Ag"

- Recombinant antigen produced in CHO cells
- Truncated with a deletion of 77 a.a anchor domain
- B cell and CD4+ T cell epitopes

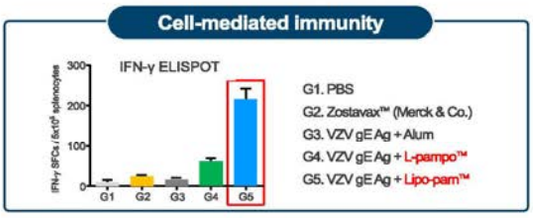
CVI-VZV-001: Superior Efficacy Over Existing Herpes Zoster Vaccines

CHA Vaccine Institute 주식회사 지에스신약연구소

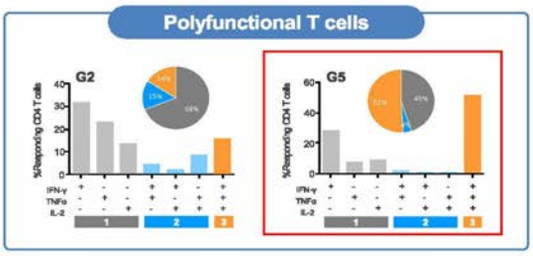
CVI-VZV-001, a Lipo-pam™-adjuvanted vaccine, demonstrates higher efficacy, with higher cell-mediated immunity and polyfunctional T cells

CVI-VZV-001 vs. a live-attenuated vaccine (Zostavax™, Merck & Co.)

Cell-mediated immunity

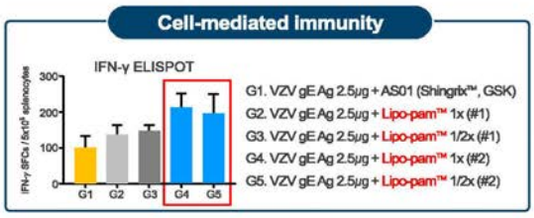


Polyfunctional T cells

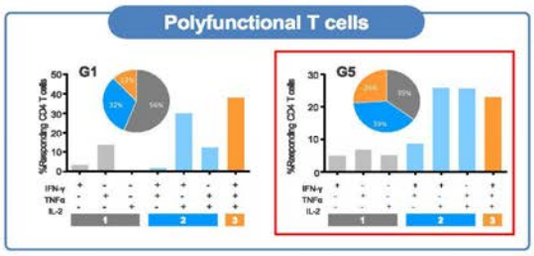


CVI-VZV-001 vs. a recombinant vaccine (Shingrix™, GSK)

Cell-mediated immunity



Polyfunctional T cells



CVI-Flu-001: An Influenza Vaccine for the Elderly in Preclinical Studies

CHA Vaccine Institute 주식회사 차백신연구소

L-pampo™ adjuvanted CVI-Flu-001 is designed to induce higher Ab production and long-lasting responses in the elderly

- Quadrivalent flu vaccine (split virion, inactivated)
- Two A subtypes & Two B types
- Collaboration program

CHA Vaccine Institute 주식회사 차백신연구소

CVI-Flu-001

Seasonal Flu vaccine "HA Antigens from 4 flu viruses"

Potent Adjuvant "L-pampo™"

- Complex of TLR2 &TLR3 ligands
- Synergistic effects in inducing both humoral & cellular immune responses
- Strong Th1 immune response

Enhanced Flu vaccine efficacy for elderly

Advantages

- Higher HI Titers and CMI
- Long Lasting Response
- Sparing Antigen Dose

CHA Vaccine Institute, Co., Ltd. 17

CVI-NoV-001: L-pampo™ Adjuvanted Norovirus VLP Vaccine Program

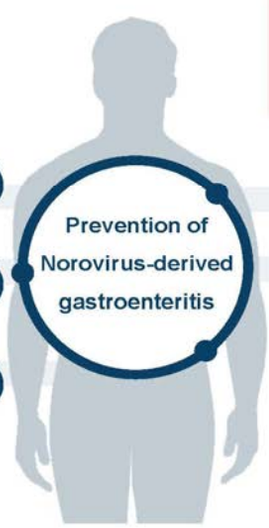
CHA Vaccine Institute 주식회사 차백신연구소

Multivalent Norovirus VLP vaccine platform: Robust humoral, cellular, and mucosal immunity able for cross-protection against various genotypes

- Inducing mucosal immunity
- Dual acting (Ag delivery & Immune booster)
- Robust CMI response
- Proven safety by CVI adjuvanted vaccine studies

Advantages

- Inducing neutralizing Ab
- Inducing mucosal immune response
- Inducing strong CMI



Prevention of Norovirus-derived gastroenteritis

Potent adjuvant "L-pampo™" "Lipo-pam™"

Various Ag types "Norovirus VLP"

CHA Vaccine Institute 주식회사 차백신연구소

CVI-NoV-001

- Multivalent VLP antigens produced by Baculovirus expression systems
- GI.1, GI.3, GII.2, GII.4 consensus sequences

CHA Vaccine Institute, Co., Ltd. 18

CVI-SL-CoV-001: Sublingual COVID-19 Vaccine

CHA Vaccine Institute 주식회사 차백신연구소

A subunit vaccine targeting mucosal immunity,
which is safer, more effective, and more convenient than existing COVID-19 vaccines

- Inducing humoral & cellular immune responses
- Respiratory mucosal immunity

Advantages

- Needle-free administration
- Reducing distribution cost
- Inducing mucosal immune response

Prevention of COVID-19 disease in LMICs

Potent adjuvant "L-pampo™"

Sublingual delivery system

Ag types "RBD of VOCs"

CHA Vaccine Institute 주식회사 차백신연구소
CVI-SL-CoV-001

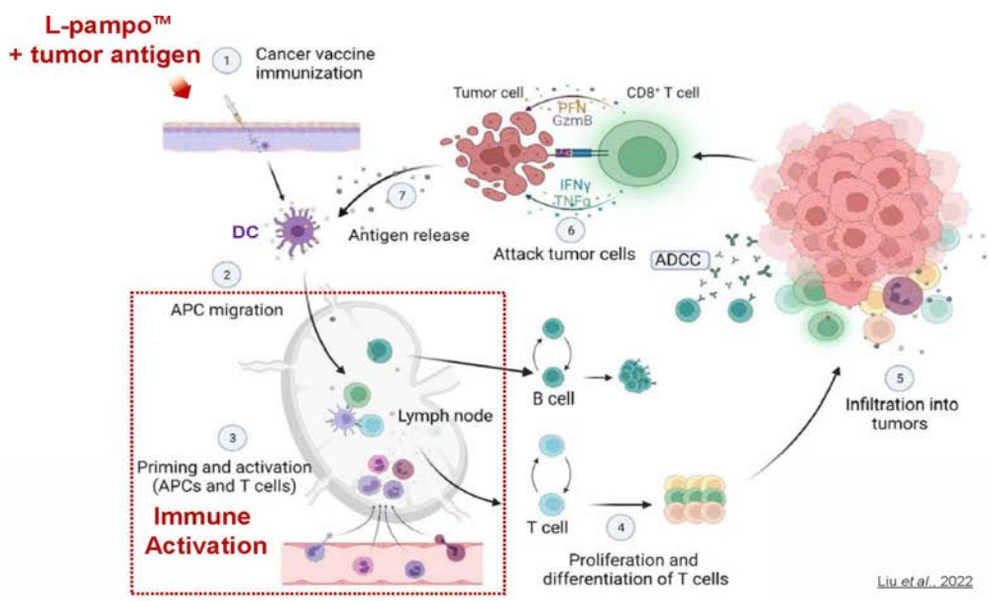
- SARS-CoV-2 delta variant RBD antigen
- Sublingual delivery system provided by BioLingus

CHA Vaccine Institute, Co., Ltd. 19

L-pampo™, a Potent Cancer Vaccine Adjuvant

CHA Vaccine Institute 주식회사 차백신연구소

L-pampo™, a potent cancer vaccine adjuvant, promotes robust tumor antigen-specific T-cell immune responses in the Tumor-Immunity Cycle induced by cancer vaccines



CHA Vaccine Institute, Co., Ltd. 20

Collaboration Opportunity Summary

CHA Vaccine Institute |주| 차백신연구소

1

L-pampo™ & Lipo-pam™ Platform Technology
- Synergistically Induces Humoral and Cellular Immune Responses
- Therapeutic Potential by Eliciting a Strong Th1 Immune Response
- Platform Clinically Proven Mature: Phase 2b

2

Huge Market Potential with Disruptive Approaches
- First-in-Class Therapeutic Vaccine for Chronic Hepatitis B
- Best-in-Class Prophylactic Vaccine for Hepatitis B Virus
- Best-in-Class Prophylactic Vaccine for Herpes Zoster
- Best Immune Checkpoint Inhibitor Combination Therapy to Overcome Resistance to ICI Therapy

3

CHA Vaccine Institute is Seeking Collaboration Partners
- Co-development & Out-licensing of CVI's Existing Pipelines
- Co-development of Combination Therapy with CVI's Pipelines
- Collaboration to Develop Novel Immunotherapies with CVI's Platform Technologies

CHA Vaccine Institute Co., Ltd. _ 21

CHA Vaccine Institute |주| 차백신연구소

THANK YOU

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CHA Vaccine Institute, Co., Ltd. 22

02

감염병 백신 개발을 위한 SKY mRNA 플랫폼

신진환 실장
SK바이오사이언스

Speaker

Jinan Shin

- SK bioscience
- Vice President

EDUCATION:

- 2020 Ph.D. in Pharmacy, School of Pharmacy, Sungkyunkwan University
- 2004 M.S. Biological Science, KAIST
- 2002 B.S. Genetic Engineering, Korea University

PROFESSIONAL EXPERIENCE:

- 2018 ~ Present SK bioscience
- 2008 ~ 2018 SK Chemicals
- 2004 ~ 2008 Hanmi Pharmaceutical

Topic

SKY mRNA Platform for Prophylactic Vaccine Development

Abstract

Introduction: SK initiated research into mRNA vaccines in response to the COVID-19 pandemic. In a relatively short period, the company secured its mRNA platform and undertook research and development for infectious diseases such as Covid, Japanese Encephalitis Virus (JEV*) and Respiratory Syncytial Virus (RSV). The SKY mRNA platform incorporated proprietary UTR combinations and poly A-tail modifications to enhance antigen expression, mRNA stability, and process convenience. With improved protein expression and process convenience, the platform now encompasses clinical-scale GMP production processes and analytical methods.

Methods: Using the SKY mRNA platform, antigens for JEV and RSV were introduced to generate vaccine candidates. These candidates were administered to mice or rats to induce in vivo immune responses. Total antibody levels were assessed through ELISA, while neutralizing antibodies were evaluated using Focus Reduction Neutralization Test (FRNT) and Plaque Reduction Neutralization Test (PRNT). T-cell activity was examined through Intracellular Cytokine Staining (ICS) and Enzyme-Linked ImmunoSpot (ELISPOT). The efficacy of the vaccines was validated through a Challenge study.

Results: In all groups administered with the JEV vaccine candidate, effective total antibody and neutralizing antibody formation were confirmed through ELISA and FRNT analyses. T-cell activity was verified through cytokine analysis. Ultimately, in the Challenge study using a lethal dose of JEV virus, all groups vaccinated with the JEV mRNA vaccine candidate showed no pathological signs, confirming the efficacy of the vaccine candidate.

For the RSV vaccine candidate, analysis using ELISA and PRNT confirmed the induction of total antibodies and neutralizing antibodies in the vaccinated groups. Ongoing research is focused on developing a vaccine utilizing a novel form of prefusion antigen for RSV. Conclusions: By applying antigens of diverse infectious diseases such as Covid, JEV, and RSV to the SKY mRNA platform, reproducibility in production processes and in vivo immunogenicity were validated. This platform technology secures the foundation for developing prophylactic vaccines. The SKY mRNA platform is poised to play a crucial role in the rapid and effective development of vaccines in response to emerging infectious diseases in the future.

(*:The Japanese Encephalitis Virus (JEV) research project is being conducted with sponsorship from CEPI.)

International Conference USJCMSP
SK Bioscience

SKY mRNA Platform for Prophylactic Vaccine Development

Jinan Shin, Ph.D. Vice President

Mar 2024

SK Group – Biopharmaceuticals Portfolio

SK bioscience

from Prevention

SK bioscience — **Vaccine business** across R&D, process dev., manufacturing, and commercialization

Pangyo R&D Center
- Diverse Vaccine Platform
- PD, Analytical, Serology
- 650 FTE

Andong L-House Plant
- High Flexible Single Use System
- Multi-Modular system
- 390 FTE

to Cure

SK chemicals	Pharma R&D and manufacturing
SK plasma	Plasma fractionization and blood products
SK biopharmaceuticals	Novel biopharmaceutical ther apeutics R&D
SK pharmteco	Biopharma CDMO including CGT and API

SK bioscience – Upgrading R&D/Mgf. Infra

SK bioscience

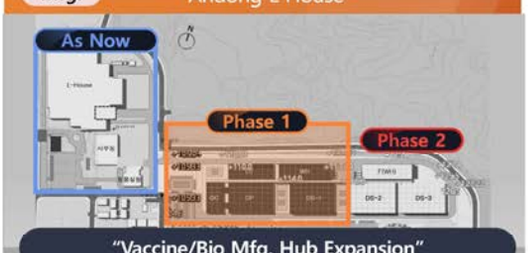
R&D Songdo Global R&PD Center

"Global Hub for bio R&D"

- Pangyo R&D Center's seamless R&D and process development excellence

- Global hub for R&D ecosystem for top-tier partners
- Upgraded R&D infra & scale by 1st half 2025

Mfg. Andong L House



"Vaccine/Bio Mfg. Hub Expansion"

- Diverse and agile manufacturing capacities (Bacterial suits, Vial suits and Fill & Finish)

- Globally qualified EU GMP and cGMP readiness
- Top tier technology platform (mRNA, small footprint and modular system)

CONTENT OVERVIEW

SK bioscience

SKBS mRNA Manufacturing Platform

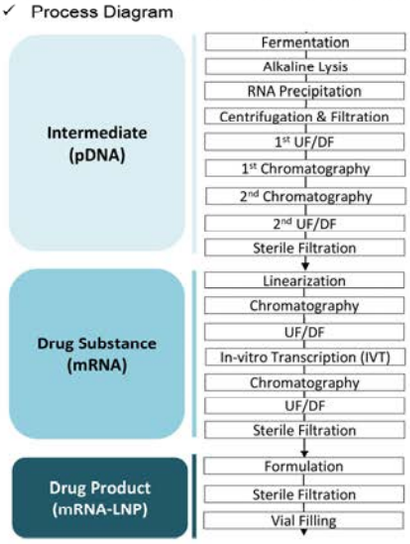
Platform for mRNA Vaccine

SKY mRNA Manufacturing Platform

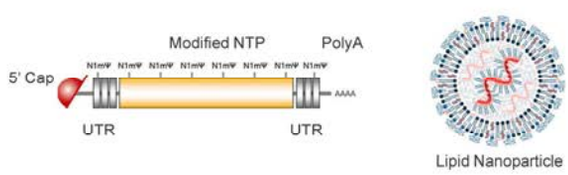
SK bioscience

Process Development

✓ Process Diagram



✓ mRNA Platform



✓ Scaling Up from the Lab to a GMP Facility

SKY mRNA Manufacturing Platform

SK bioscience

Analytical Method Development

✓ Analytical Methods for Drug Substance, DS (mRNA)

Category	Quality Attributes	Analytical Methods
General	Appearance	Appearance
	pH	Potentiometry
Safety	Bioburden	Bioburden
	Bacterial Endotoxin	Kinetic turbidimetric assay (LAL assay)
Purity	mRNA Integrity	Capillary Gel Electrophoresis
	dsRNA	ELISA
Contents	mRNA Content	Fluorescence assay
Integrity	% of 5' Cap	RP-UPLC
	% of Poly A Tail	RP-UPLC (TBD)
Identity	mRNA Sequence	PCR & Sanger sequencing
Process-related Impurity	Residual DNA template	RT-PCR & Sequencing

✓ Analytical Methods for Drug Product, DP (mRNA-LNP)

Category	Quality Attributes	Analytical Methods
General	Appearance	Appearance
	pH	Potentiometry
	Visible particle	Particles
	sub-visible particle	Subvisible particulate matter
	Osmolality	Osmometry
Excipients	LNP Size	Dynamic light scattering
	LNP Polydispersity	Dynamic light scattering
Purity	mRNA Encapsulation	Fluorescence assay
	mRNA Integrity	CGE
Content	mRNA Content	Fluorescence assay
Identity	Identity of encoded mRNA Sequence	
Excipients	Ionizable lipid Content	HPLC-CAD
	PEG-lipid Content	
	DSPC Content	
	Cholesterol Content	
	Lipid Identity	
Potency	In-vitro Expression	Cell based assay
	PRNT	PRNT
Safety	Bacterial Endotoxin	Kinetic turbidimetric assay (LAL assay)
	Sterility	Sterility
General	Extractable Volume	Volume of injections in containers
	Container Closure Integrity	Dye incursion

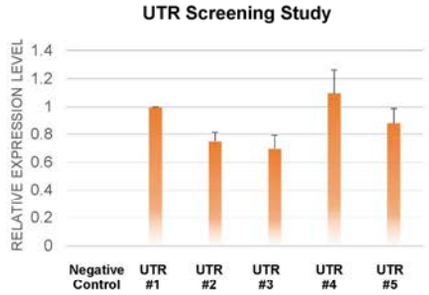
SKY mRNA Platform Development

SK bioscience

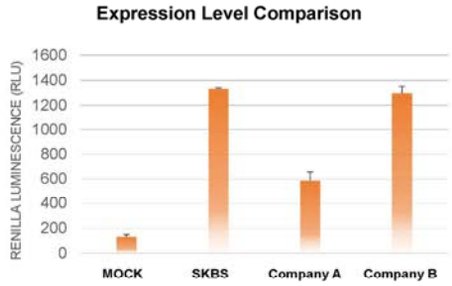
SKBS UTR System – Translation Efficiency

✓ Securing UTR platform for enhanced expression:
✓ Cell-Based Assay: Confirming expression levels in vitro using a reporter in cell-based assays.
✓ Animal Study: Validating effective efficacy in vivo for various antigens.

UTR Screening Study



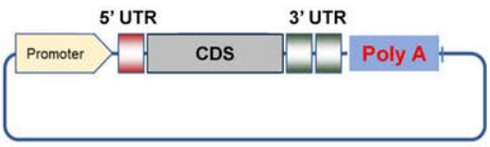
Expression Level Comparison

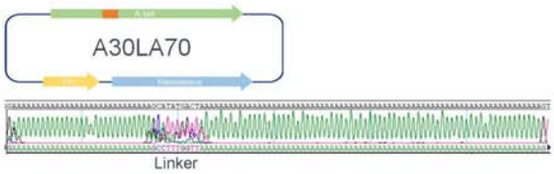


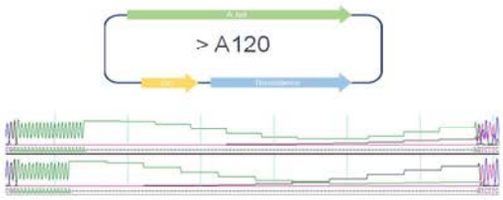
SKY mRNA Platform Development

SK bioscience

Poly A tailing

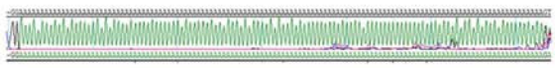






- ✓ Cloning more than 100 consecutive A stretches into pDNA results in deletions, making stable maintenance challenging.
- ✓ Frequent deletion of adenine repeat during cloning and fermentation

- ✓ SKBS platform: E.coli strain, Culture media, Culture condition optimization
- ✓ Maintaining stability is possible with more than 120 consecutive A stretches in the cell stock.



SK bioscience

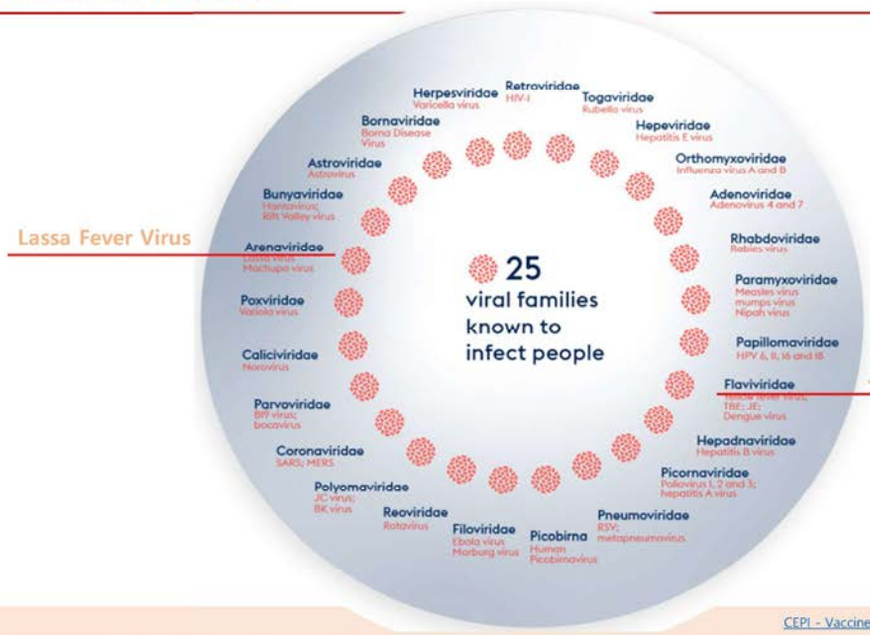
CEPI

Japanese Encephalitis Virus mRNA vaccine

CEPI-funded mRNA Vaccine Project

The Viral Most Wanted

CEPI SK bioscience



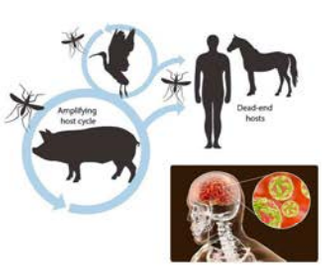
CEPI - Vaccine libraries provide head start on the next Disease X

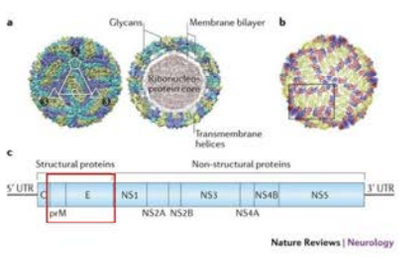
JEV Vaccine Development (CEPI Funding)

CEPI SK bioscience

Japanese Encephalitis Virus

- ✓ Japanese encephalitis virus (JEV) is a flavivirus transmitted by mosquitoes, similar to dengue, yellow fever, and West Nile viruses.
- ✓ It's a leading cause of viral encephalitis in Asia, with an estimated 68,000 clinical cases annually and a high case-fatality rate of up to 30%.
- ✓ Survivors may experience permanent neurological or psychiatric issues in 30%–50% of cases.
- ✓ JEV affects 24 countries in the WHO South-East Asia and Western Pacific regions, putting over 3 billion people at risk of infection.
- ✓ While there's no cure, treatment focuses on symptom management. Vaccines are available and recommended by WHO for areas where JE is a public health concern, aiming to integrate JE vaccination into national immunization schedules.
- ✓ SK Bioscience has applied the SKY mRNA Platform to develop a JEV mRNA vaccine for public health, supported by funding from CEPI.



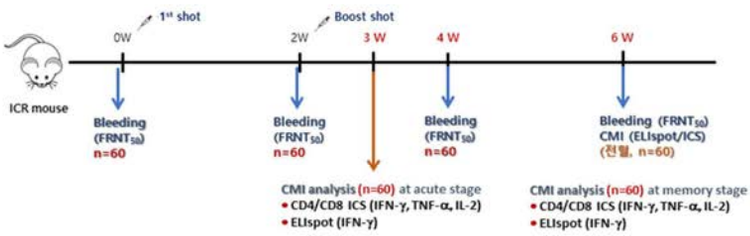


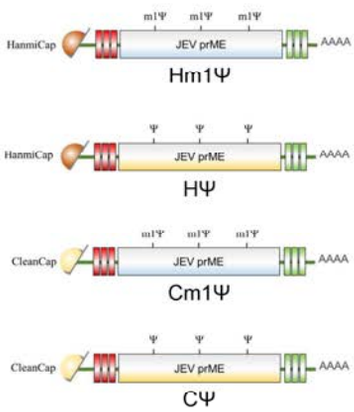
JEV Vaccine Development (CEPI Funding)

CEPI SK bioscience

Preclinical Animal Study (Humoral & cellular immunity)

- ✓ The test articles were manufactured using either HanmiCap or CleanCap and Modified UTP. (HanmiCap supplied by Hanmi Fine Chemical and CleanCap supplied by TriLink).
- ✓ The humoral and cellular immune responses of the vaccine candidates were evaluated using ICR mice.





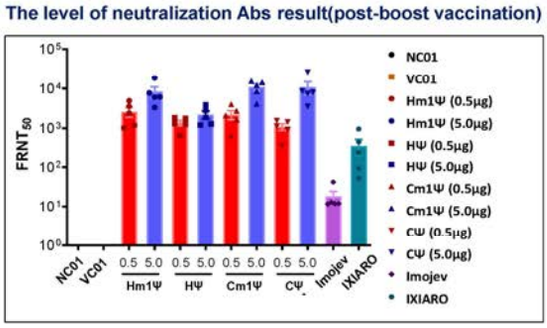
JEV Vaccine Development (CEPI Funding)

CEPI SK bioscience

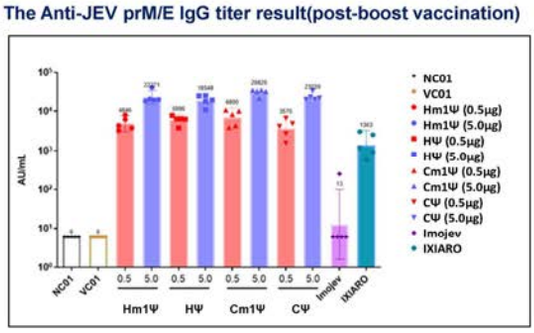
Humoral Immunogenicity - Antibody Evaluation

- ✓ FRNT and ELISA assays were conducted to assess antibody response.
- ✓ All tested mRNA JEV candidates exhibited higher antibody titers compared to comparator vaccines.
- ✓ A positive correlation was observed between neutralization and total antibody titers, indicating the potential effectiveness of mRNA JEV candidates in inducing robust immune responses.

The level of neutralization Abs result(post-boost vaccination)



The Anti-JEV prM/E IgG titer result(post-boost vaccination)

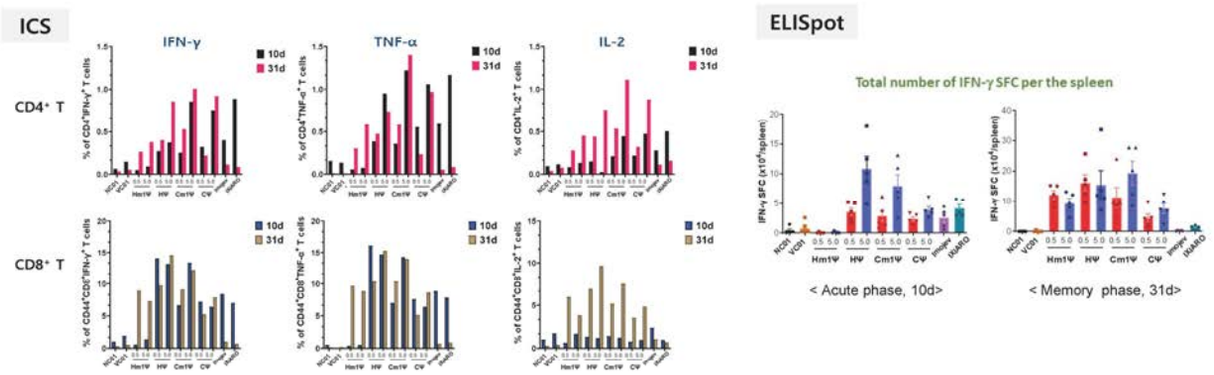


JEV Vaccine Development (CEPI Funding)

CEPI SK bioscience

Immunogenicity Study – Cell Mediated Immunity (ICS, ELISpot)

- ✓ Intracellular Cytokine Staining (ICS) and ELISpot assays were performed to assess cellular immune response.
- ✓ SK-JEV mRNA candidates were found to elicit CD4+ and CD8+ T cell responses from 10 to 31 days post-vaccination.
- ✓ Additionally, SK-JEV mRNA exhibited prolonged T cell responses and higher levels of IFN-γ compared to comparator vaccines.

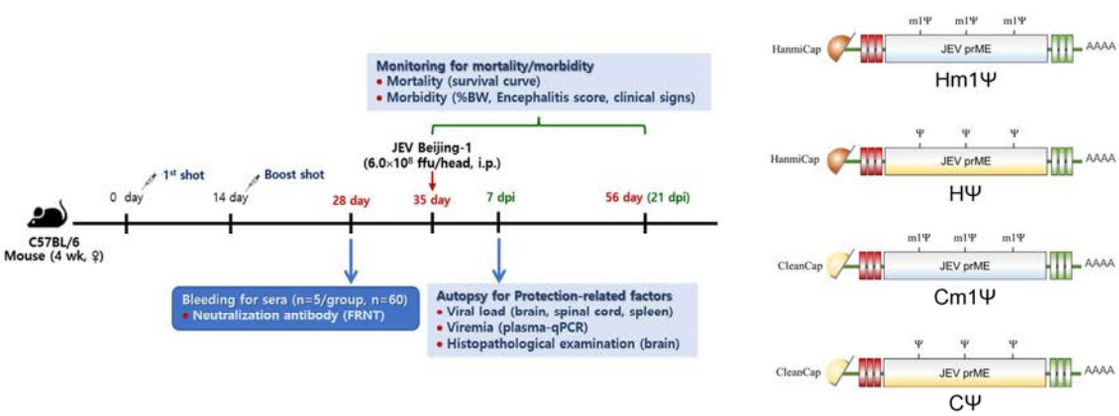


JEV Vaccine Development (CEPI Funding)

CEPI SK bioscience

Preclinical Animal Study (Effectiveness (Protective))

- ✓ Test articles were synthesized utilizing either HanmiCap or CleanCap with Modified UTP, where HanmiCap was procured from Hanmi Fine Chemical and CleanCap from TriLink.
- ✓ Effectiveness studies were performed utilizing C57BL/6 mice and the JEV Beijing-1 strain.

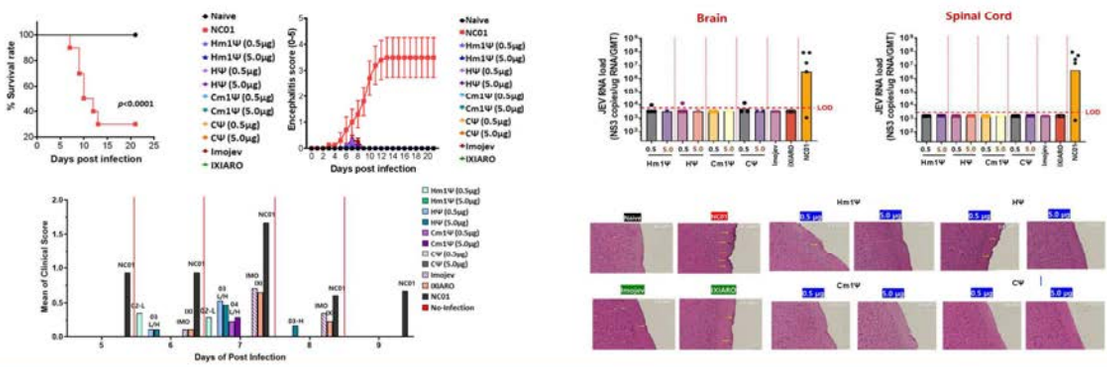


JEV Vaccine Development (CEPI Funding)

CEPI SK bioscience

Effectiveness

- ✓ Both SK-JEV mRNA and comparator vaccines demonstrated exceptional protective efficacy, with no observed mortality at a dose of 6 x 10^8 ffu/head via intraperitoneal administration.
- ✓ Particularly noteworthy was the expedited recovery trend of clinical symptoms observed in the SK-JEV mRNA group compared to the comparator vaccines.
- ✓ Viral RNAs in the central nervous system (CNS) were undetectable (below the limit of detection) in both the SK-JEV mRNA and comparator vaccine groups.
- ✓ Additionally, only mild cellular infiltration was observed in a minority of individuals from both groups, suggesting the absence of actual encephalitis or significant brain tissue damage.



SK bioscience

Respiratory Syncytial Virus mRNA vaccine

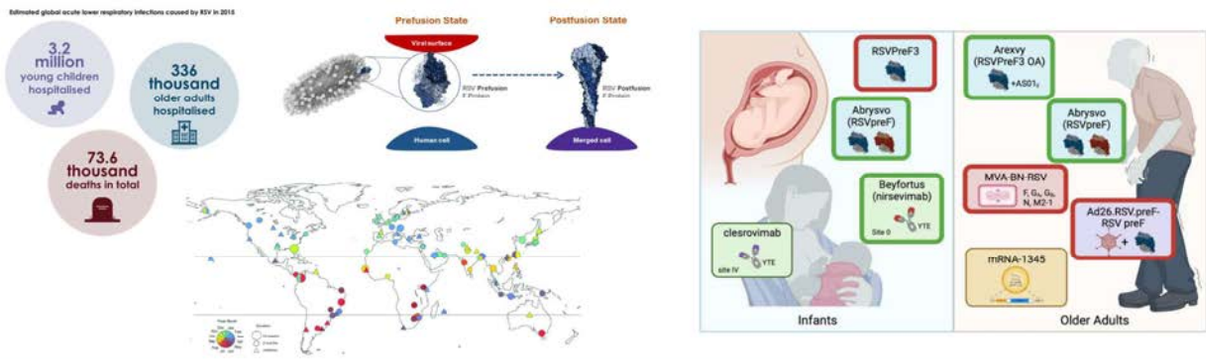
SK Bioscience mRNA Vaccine Project

RSV Vaccine Development

SK bioscience

Respiratory Syncytial Virus

- ✓ Human respiratory syncytial virus (RSV) is a common virus that causes respiratory tract infections in people of all ages.
- ✓ In infants and young children, RSV can cause severe bronchiolitis, which can sometimes be fatal.
- ✓ Since infections do not provide complete immunity, they are usually not serious, but reinfection is common.
- ✓ Recently, GSK's Arexvy and Pfizer's Abrysvo are approved for people aged 60 years and older.
- ✓ SK bioscience applied SKY mRNA Platform and own prefusion mutation for RSV vaccine development



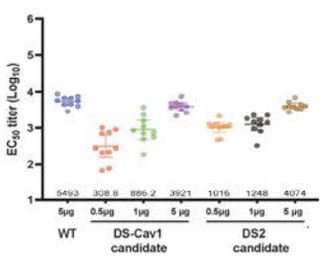
RSV Vaccine Development

SK bioscience

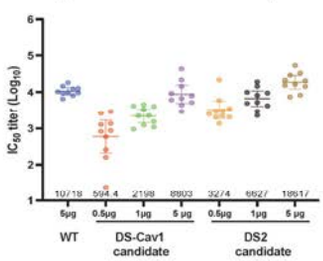
Respiratory Syncytial Virus

- ✓ Previously Known Prefusion mutant forms (DS-Cav1 and DS2) were applied to SKY mRNA platform.
- ✓ FRNT and ELISA assay conducted to evaluate antibody response.
- ✓ Successful neutralization and total antibody response observed in SKY mRNA Platform.
- ✓ Neutralization antibody response of mRNA vaccine was comparable to that of subunit vaccine
- ✓ SK Bioscience will apply own prefusion mutation for preclinical test

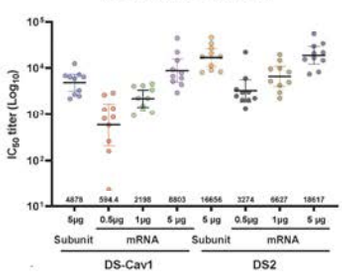
The Anti-RSV IgG titer result



The level of neutralization Abs result (post-boost vaccination)



The level of neutralization Abs result (Subunit vs mRNA)



SK bioscience

Further Plan

mRNA therapy

Further Development

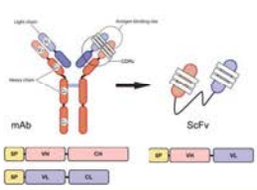
SK bioscience

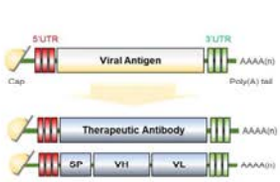
Prophylactic Vaccine

- ✓ Japanese encephalitis virus (JEV) vaccine
  - Evaluation of safety and stability of JEV vaccine candidate is underway.
  - IND filing and Phase 1 trials are scheduled for 2024.
- ✓ Respiratory syncytial virus (RSV) vaccine
  - Immunogenicity of SK's prefusion mutation will be assessed.
  - Following the selection of the RSV vaccine candidate, NCS study will be conducted.

mRNA therapies

- ✓ Antibody therapies have become an important class of therapeutics in recent years.
- ✓ SK Bioscience plans to utilize scFv (single-chain variable fragment) with its SKY mRNA platform.
- ✓ It is anticipated that mRNA antibodies will expand treatment options for a broader range of patients..





03

RSV 백신 연구개발 전략

김석규 이사
유바이오로직스

Speaker

Seok-Kyu Kim

- EuBiologics
- Director / Head of Business Development

EDUCATION:

- 2012 MBA, Korea University

PROFESSIONAL EXPERIENCE:

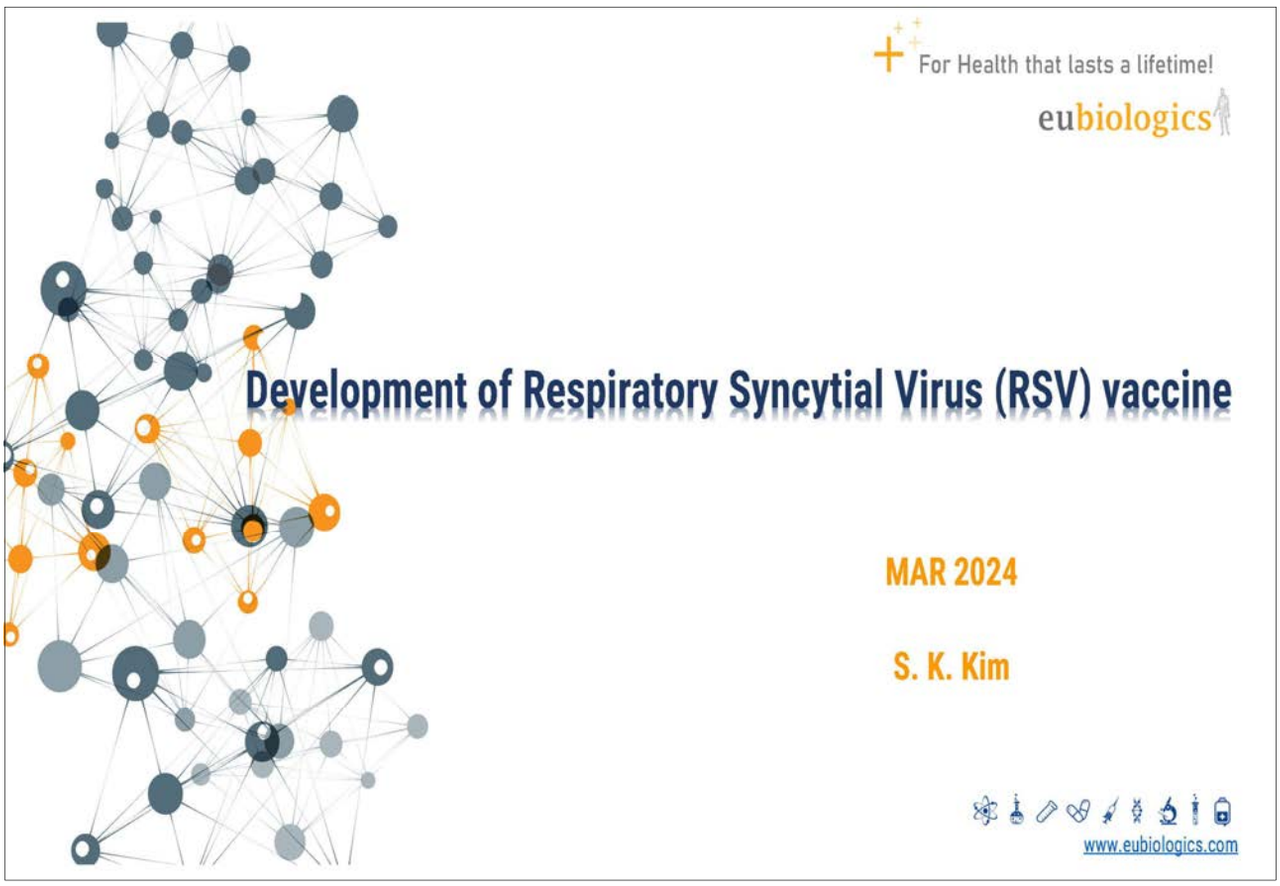
- 2018 ~ Present Director, EuBiologics
- 2007 ~ 2018 Professional, LG Chem

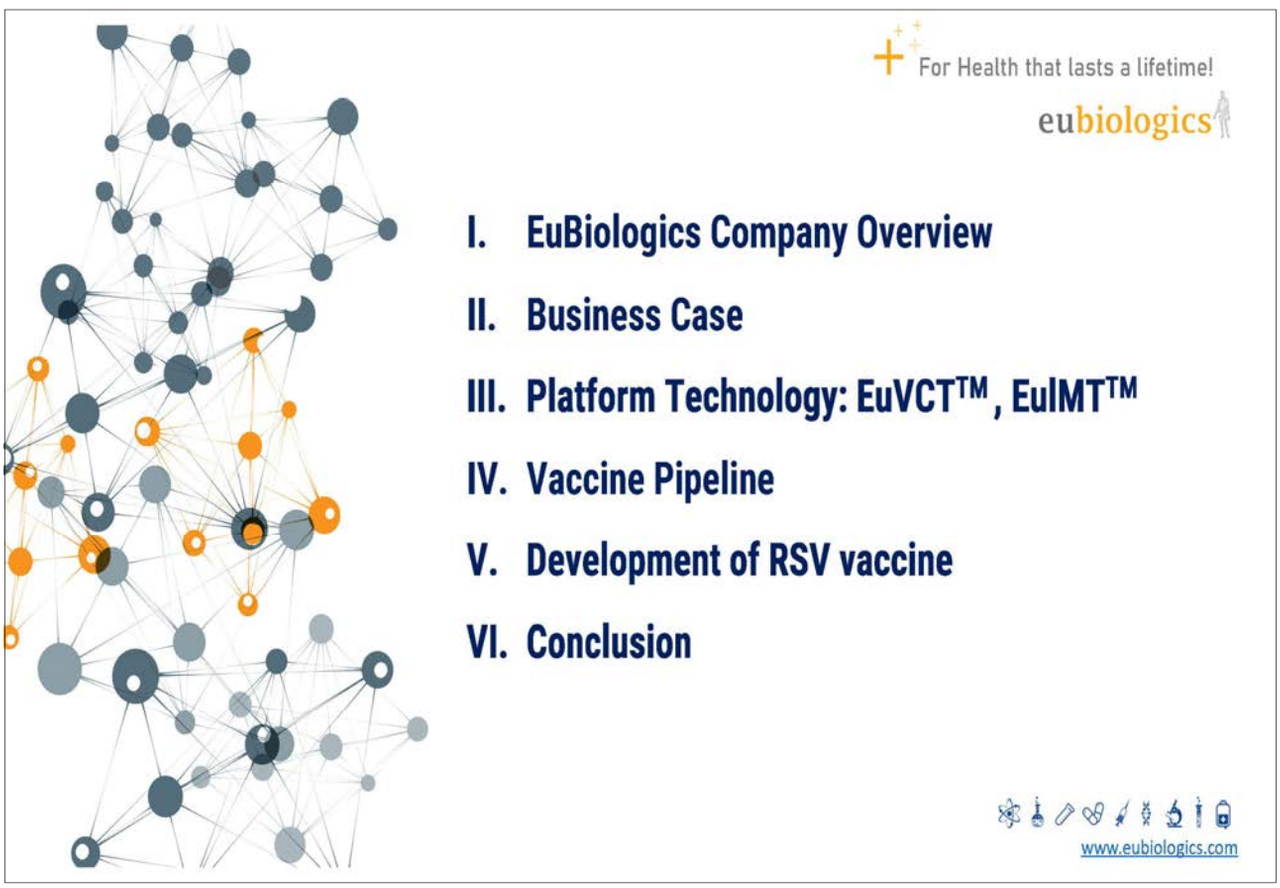
Topic

EuBiologics' Vaccine Platform & RSV Vaccine Development

Abstract

In order for effective vaccine development, there must be a distinctive vaccine platform others could not. EuBiologics is currently advancing the development of an RSV vaccine using its own TLR-4 Agonist (MPLA) adjuvant(immune enhancer) produced in-house, and SNAP (Spontaneous Nano-liposome Antigen Particle) technology, enabling the prompt antigen display in liposomes. All non-clinical trials have been successfully completed and EuBiologics obtained phase 1 IND approval from the Korean Ministry of Food and Drug Safety in January 2023. In this presentation, I aim to introduce Eubiologics' cutting-edge vaccine platform, its diverse vaccine development portfolio, and the results from the non-clinical research on the RSV vaccine.


For Health that lasts a lifetime!
eubiologics
Development of Respiratory Syncytial Virus (RSV) vaccine
MAR 2024
S. K. Kim
www.eubiologics.com


For Health that lasts a lifetime!
eubiologics
I. EuBiologics Company Overview
II. Business Case
III. Platform Technology: EuVCT™, EuIMT™
IV. Vaccine Pipeline
V. Development of RSV vaccine
VI. Conclusion
www.eubiologics.com

I. EuBiologics Company Overview

eubiologics

EuBiologics is a publicly traded biopharmaceutical company based in South Korea focusing on vaccine development and supply, immuno-therapeutics development for global public health.

Company Profile

Establishment	10th March, 2010
Business Place	HQ: Seoul, South Korea Facility - Two Manufacturing sites in Chuncheon - R&D Center in Chuncheon
No. of Employee	Over 320
Market Capital	USD 340M Listed in KOSDAQ since Jan 2017
Business Area	- Vaccine Development, Manufacturing & Supply - CRMO(Contract R&D and Manufacturing Organization)

Plant

[C-Plant]

[V-Plant, R&D Center]

[Facility and Capacity]

- C Plant : Oral Cholera Vaccine-DS & DP (33M doses/y)
  : EuCorvac-19 Vaccine-DS (200M doses/y, 1,000L*2 lines of Animal cell culture line)
- V Plant : Bacterial Vaccine Line- DS(Total 200M doses/y)
  → rCRM197, TCV, MCV, PCV and others
  : Oral Cholera Vaccine-DS & DP (32~50M doses/y)
  -under construction by support of BMGF
  : CMO for API ; Suite#4, 5 (50/100/200/500/1,000-L Lines)

II. Business Case: OCV & Public Vaccines

eubiologics

EuBiologics becomes the largest supplier of oral cholera vaccine(EuVichol-Plus) shipping over 110M doses to LMICs through UNICEF, as a result of successful public/private product development partnership.
EuBiologics has continued to scale-up and developed programmatically suitable presentation and new vaccines at affordable pricing to meet the needs of public markets and responds to infectious diseases outbreak promptly.

Date	OCV Development History
Sep 2010	OCV License Agreement with International Vaccine Institute
Aug 2014	Non-inferiority trial (Euvichol vs Shanchol) in the Philippines
Dec 2015	**Euvichol WHO PQ** (6M doses per annum)
Sep 2016	PQ variation approval (600L scale-up allowing 25M & thimerosal removal)
Aug 2017	PQ variation approval **(Plastic Tube)**
~2024	Expects Euvichol-S (Simplified) PQ achieving cost reduction & capacity increase
~Jun 2025	Scale up for DS and DP ongoing, capacity doubled up to 80~100M funded by BMGF

Vaccine	Development Stage	Commercialization Strategy
Cholera Conjugate Vaccine	• Phase I study started in Oct 2022 • Collaboration with International Vaccine Institute and Massachusetts General Hospital	• Targeting children in LMICs to complement OCV

Euvichol (Glass Vial)

Euvichol-Plus (Plastic Tube)
→ Game changer
; Weight, Volume down
; Easy Administration

II. Business Case: Immuno-stimulants

eubiologics

EuBiologics engages in active research and development in the fields of immunology and life sciences, and produces a carrier protein(rCRM197) for the polysaccharide conjugation vaccines and various adjuvant system of recombinant TLR4 agonist(MPLA) for enhancing the vaccine efficacy.

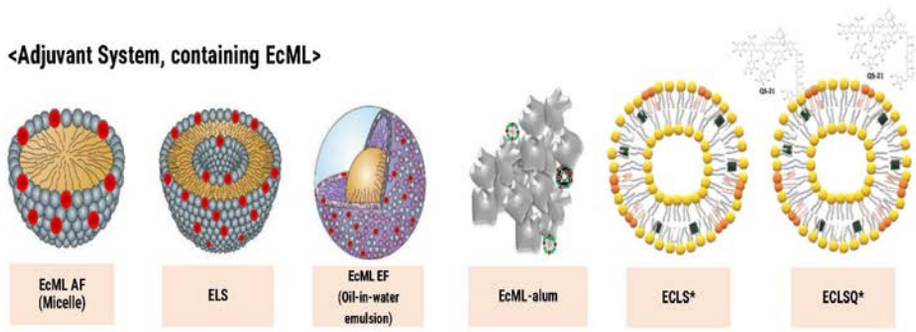
[EuCRM-197]

<Essential Material for conjugation with bacterial polysaccharides>

- Method for Production of rCRM197 by recombinant E. coli ; Patent No.: 10-2048456 (KR)
- Expression Method of CRM197 Protein ; Patent No.: 10-2099342 (KR)

[EcML]

<Adjuvant System, containing EcML>



*Collaboration with POP Biotechnologies, Inc.

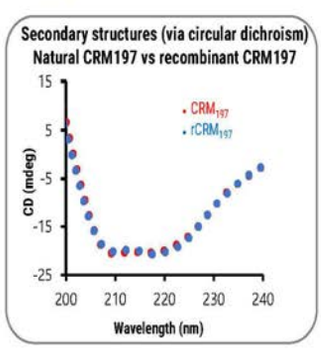
Abbreviation:
E: EcML, C: CoPoP, Q: QS21, LS: Liposome

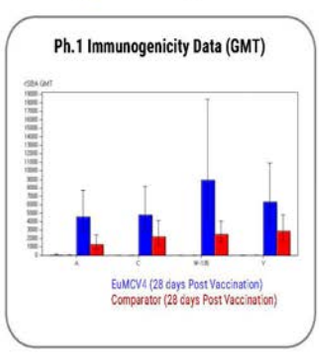
III-1. Platform Technology: EuVCT™

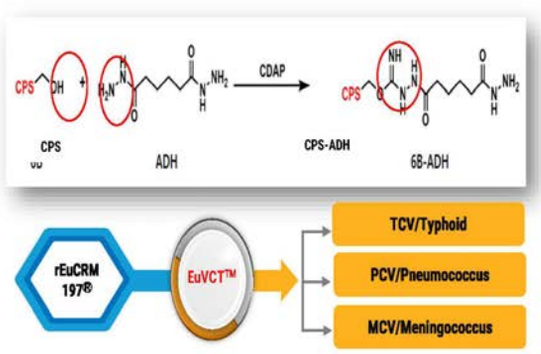
eubiologics

EuVCT™ : EuBiologics Vaccine Conjugation Technology

Development & in-house production of recombinant CRM197 and conjugation know-how leads successful development of conjugate vaccines which demonstrate higher efficacy at lower cost







Patents & Publication

1) Method for Production of rCRM197 by recombinant E. coli - Patent No.: 10-2048456 (KR)
2) Expression Method of CRM197 Protein - Patent No.: 10-2099342 (KR)
3) An open-label, comparative, single dose, clinical Phaselstudy to assess the safety and immunogenicity of typhoid conjugate vaccine (Vi-CRM197) in healthy Filipino adults.
Vaccine.2021 May 6;39(19):2620-2627. Seuk Keun Choi et al.
4) Generation of a human monoclonal antibody to cross-reactive material 197 (CRM197) and development of a sandwich ELISA for CRM197 conjugate vaccines.
J. Microbiol. Biotechnol. 2018, vol.28, no.12, pp. 2113-2120. Dain Kim et al.

III-1. Platform Technology: EuVCT™

eubiologics

Vaccine	Development Stage	Commercialization Strategy
Typhoid conjugate vaccine (EuTYPH-C)	• Completed Phase III study in the Philippines, non-inferiority demonstrated to Typbar TCV • Additional Phase III study ongoing in Africa, funded by RIGHT Foundation	• Expect PQ in 2024 • Targeting LMICs through UNICEF 
Quadrivalent Meningococcal Conjugate Vaccine(ACWY)	• Phase I study completed, safety and immunogenicity to Menveo demonstrated	• License out
Pentavalent Meningococcal Conjugate Vaccine(ACWY + X)	• Phase I study in progress • Collaboration with PATH funded by BMGF and RIGHT Foundation	• Expect PQ in 2027 • Targeting LMICs through UNICEF
Pneumococcal Conjugate Vaccine (15-valent)	• Phase I study completed	• License out

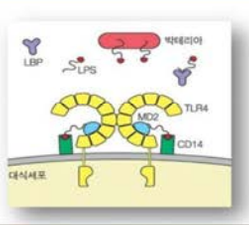
III-2. Platform Technology: EuIMT™

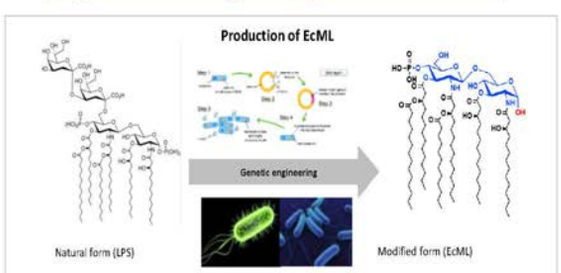
eubiologics

EuIMT™: EuBiologics Immuno-Modulation Technology

. Monophosphoryl Lipid A produced from recombinant *E.coli* (EcML)

- **A potent vaccine adjuvant** with effectiveness comparable to other MPLAs
  → Boosting immune responses by acting as a **TLR4 agonist**.
- Recombinant *E.coli* directly producing MPLA
  → **Simple manufacturing process, low cost and scalable**





1) *Bacterium producing monophosphoryl lipid A and method of producing monophosphoryl lipid A by using bacterium*
- Patent No.: 10-1761348(KR) / US10308945 (US)

2) *Bacteria constitutively producing monophosphoryl lipid A, and method for the production of monophosphoryl lipid A using the same*
- Patent No.: 10-2019331(KR) / US10557156 (US)

Product	Composition
MPL(GSK)	Heterogeneous; Hexa acyl 20~40%, Penta acyl 25~60%, Tetra acyl 15~35%, Hepta acyl ~ 0.5%
GLA(IDRI)	Homogeneous; Hexa acyl 100%
EcML (EuBiologics)	Nearly Homogeneous **Hexa acyl ≥ 90%**, **Penta+Tetra acyl 10~20%**

III-2. Platform Technology: EuIMT™

eubiologics

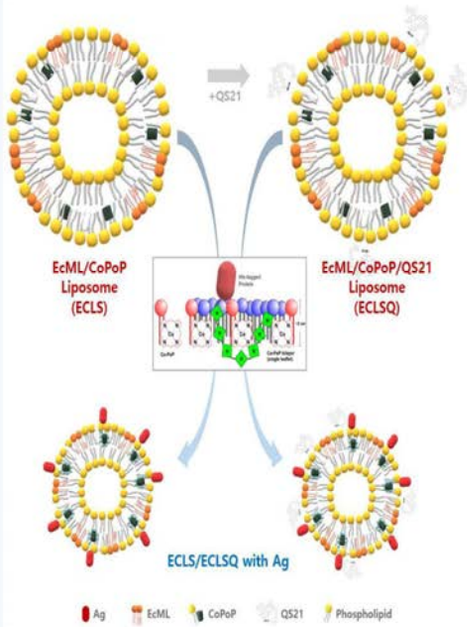
EuIMT™: EuBiologics Immuno-Modulation Technology

Potent Nanoliposome Vaccine Adjuvant: ECLS & ECLSQ

1. Nanoliposome based Adjuvant
- Similar to lipid & cholesterol in human body → **No safety concern**
- Liposome DDS(Drug Delivery System) is widely applied in the field of vaccines and therapeutics.

2. Monophosphoryl Lipid A produced from recombinant *E.coli* (EcML)
- **A potent vaccine adjuvant** with effectiveness comparable to other MPLAs
  → boosting immune responses by acting as a **TLR4 agonist**.
- Recombinant *E.coli* directly producing MPLA
  → **Simple manufacturing process, low cost and scalable**

3. Versatile Antigen Display using CoPoP (SNAP platform)
- Simple nanoparticle antigen display technology using CoPoP (similar to VLP)
- Diverse antigen anchored on the liposome surface
  → **Enhanced uptake by antigen presenting cells**



IV. Vaccine Pipeline

eubiologics

EuBiologics has a pipeline of vaccines leveraging its platform technologies, EuVCT™ and EuIMT™

Product		Discovery / Pre-clinical / Phase I / Phase II / Phase III / NDA / Launch	Remark
Euvichol /Euvichol-Plus			
EuCRM197 ™			
EuVCT	TCV[1]		Sponsored by RIGHT Foundation Grant
	PCV[2]		Open collaboration
	MCV[3]		Sponsored by Korean Gov't BMGF/RIGHT Grant
EcML™ (MPL-A, Novel Adjuvant)			
EuIMT	COVID-19		Sponsored by Korean Gov't
	HPV		Sponsored by Korean Gov't
	RSV[4]		Sponsored by Korean Gov't
	HZV[5]		Sponsored by Korean Gov't
	AD[6]		

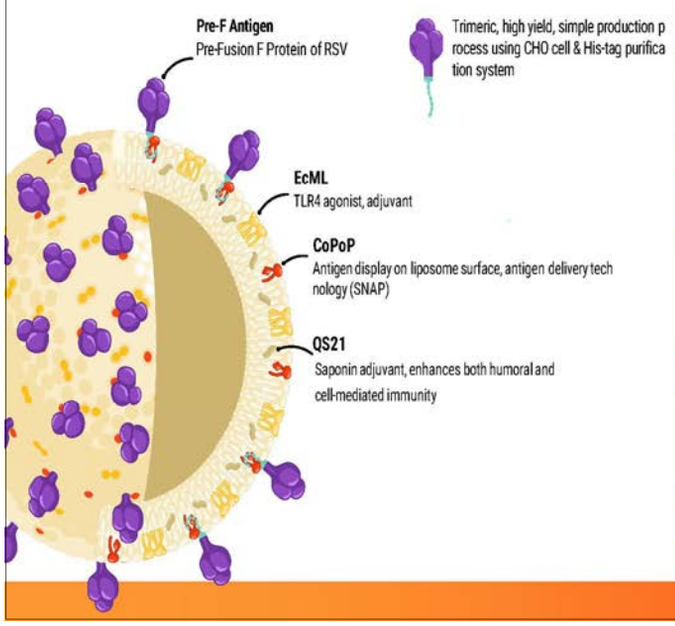
1) TCV: Typhoid Conjugate Vaccine
2) PCV: Pneumococcal Conjugate Vaccine
3) MCV: Multivalent Meningococcal Conjugate Vaccine
4) RSV: Respiratory Syncytial Virus
5) HZV: Herpes Zoster Virus
6) AD: Alzheimer Disease

V. Development of RSV vaccine: EuRSV

eubiologics

➢ EuRSV vaccine candidate, **IND approval by MFDS(Ministry of Food and Drug Safety)** on 2 January 2024

EP-RSV: Liposome-displayed Pre-fusion F Prefusion F protein of RSV



TPP(Target Product Profile)

Description	EuRSV vaccine (EuRSV vaccine combined with RSV F protein and nano-particle adjuvant)	
Strain	CHO (Chinese Hamster Ovary) cell	
Antigen	RSV Prefusion F	
Name	EuRSV-1	EuRSV-2
API	RSV F (Low & High ds)	RSV F (Low & High ds)
Excipient (adjuvant)	EcML CoPoP QS21 /0.5mL/dose	EcML CoPoP /0.5mL/dose
Dosage form	Lyophilized	
Indication	Prevention of lower respiratory tract disease (LRTD) caused by Respiratory Syncytial Virus (RSV) in elderly people over 60 years of age	
Dosing schedule	0.5mL, IM, twice in 4-week interval (TBD)	
Storage condition	2 ~ 8°C	

V. Development of RSV vaccine: strategy

eubiologics

Basic Concept of EuRSV vaccine candidate

1. RSVF-E2 Antigen: pre fusion F protein

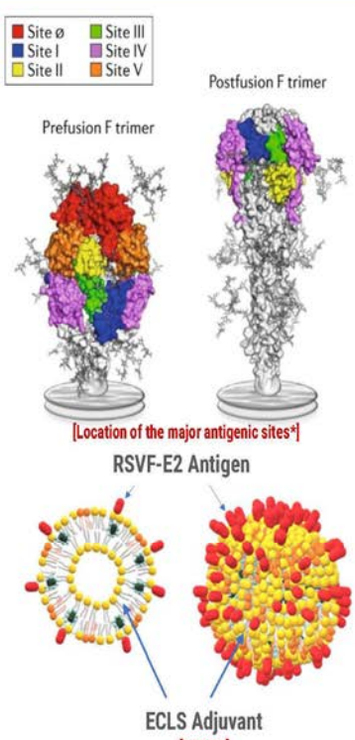
- High yield, simple production process using CHO cell & His-tag purification system

2. ECLS(+/- Q) Adjuvant (EuIMT™ : EuBiologics Immuno-Modulation Technology)

- EcML: TLR4 agonist, Adjuvant
- CoPoP: Antigen display on liposome surface
- QS-21: saponin, Adjuvant

→ Leveraging adjuvant ECLS(+/- Q), only a small amount of antigen required

3. Presentation & Storage → Lyophilized, 2-8℃



*Ref.Respiratory syncytial virus entry and how to block it_NATURE Reviews | MicRobiology, VOLUME17, APRIL 2019

VI. CONCLUSION

eubiologics

- **Efficacy Study**
  - The efficacy study of EuRSV vaccine candidate was evaluated in cotton rat, mouse animal models.
  - EuRSV vaccine candidate demonstrated **excellent humoral and cellular immunity**.
- **Toxicity Study**
  - There is **no toxicity** caused by EuRSV vaccination, suggesting its safety profile.
  - EuRSV vaccine candidate has **low risk of Vaccine-Associated Enhanced Disease(VAERD)**
- In summary, the non-clinical outcomes have led to the approval of the Phase I clinical trial by MFDS.

- **Future plan**

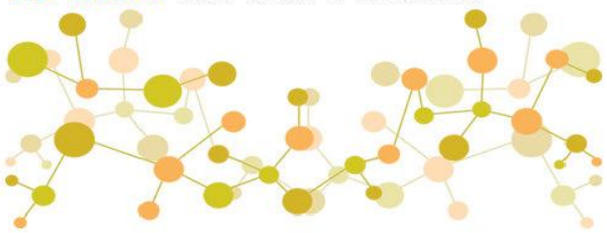
EUPOP LIFE SCIENCES Premium vaccine development FROM 'EUPOP Life Sciences'

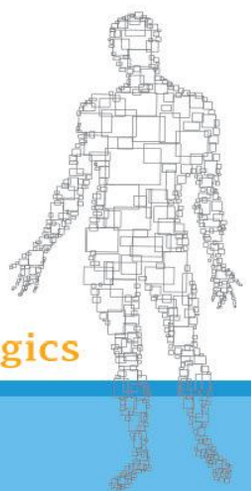
	Year	2024	2025	2026	2027
EuRSV Vaccine Development	Phase I	In KOREA			
	Phase II & III		In USA or AUS (EUPOP)		

Thank You

일생 동안 지속하는 인류의 건강에 기여

For health that lasts a lifetime!





eubiologics

본사: 서울특별시 강남구 도산대로 207 (신사동, 성도빌딩 8층)
TEL: 02. 572. 6675 FAX: 0507. 891. 2537

04

신종변이 대응 코로나19 다가백신 개발 전략

강창율 대표
셀리드

Speaker

Chang-Yuil Kang

- Cellid Co., Ltd.
- Chief Executive Officer

EDUCATION:

- 1987 Ph.D.in Immunology(State University of New York at Buffalo, USA)
- 1981 M.S.in Microbiology/Pharmacy (SeoulNational University, Seoul, Korea)
- 1977 B.S.in Pharmacy (Seoul National University, Seoul, Korea)

PROFESSIONAL EXPERIENCE:

- 2014 ~ Present Chief Executive Officer, Cellid Co., Ltd.
- 2020 ~ Present Professor Emeritus, College of Pharmacy, Seoul National University
- 2020 ~ Present Non-Executive Director, Handok Co., Ltd.
- 1994 ~ 2020 Professor, College of Pharmacy, Seoul National University
- 2009 ~ 2010 Team Leader of T/F, Bio-Medical Dep, Presidential Council for Future & Vision
- 2005 ~ 2005 Secretary-General, International Society of Cytokines.
- 2003 ~ 2004 President, Korean Society of Immunizations
- 1987 ~ 1994 Scientist, IDEC Pharmaceutical Corporation(Currently, Biogen-IDEC), USA

Topic

Strategy to develop effective multivalent COVID-19 vaccines against emerging variants based on adenovirus vector platform

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron strain has evolved into highly divergent variants. We developed chimeric adenoviral vector (Ad5/35)-based coronavirus disease 2019 (COVID-19) vaccines, which are replaced with a serotype 35 fiber based on the backbone of serotype 5 adenovector for better antigen delivery. Our vaccine can effectively deliver spike genes to antigen-presenting cells through CD46 binding, which leads to effectively stimulating CD4+ T cells, CD8+ T cells, and B cells in either direct or indirect ways. Our AdCLD-CoV19-1 OMI vaccine, encoding the spike protein of the BA.1 variant, is currently in Phase 3 clinical trials. Additionally, we developed multivalent Omicron variant-specific vaccines using phylogenetic trees and antigenic cartography and demonstrated their superior ability to neutralize a wide range of variants in mice and macaques. These data suggest that the developed multivalent vaccines enhance immunity against circulating Omicron subvariants and effectively elicit neutralizing antibodies across a broad spectrum of SARS-CoV-2 variants.Our ongoing research explores combinations of next-generation multivalent vaccines to confer broad protection against newly emerging subvariants.

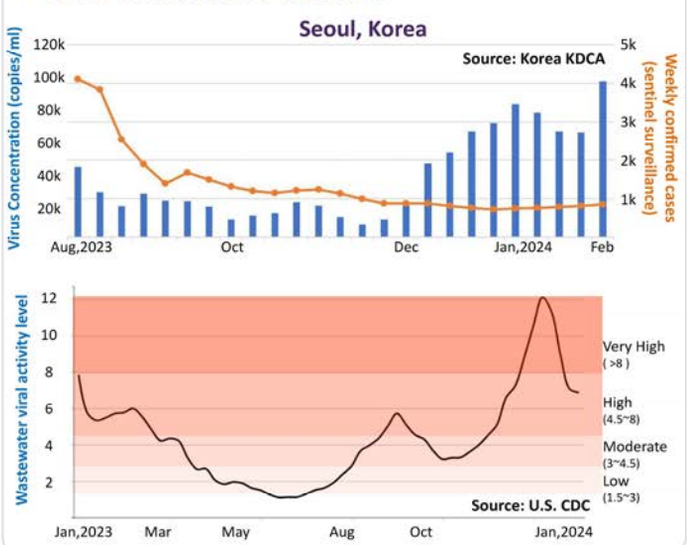
CELLID
LEADER IN CELL-BASED THERAPEUTIC VACCINE

Strategy to develop effective multivalent COVID-19 vaccines against emerging variants based on adenovirus vector platform

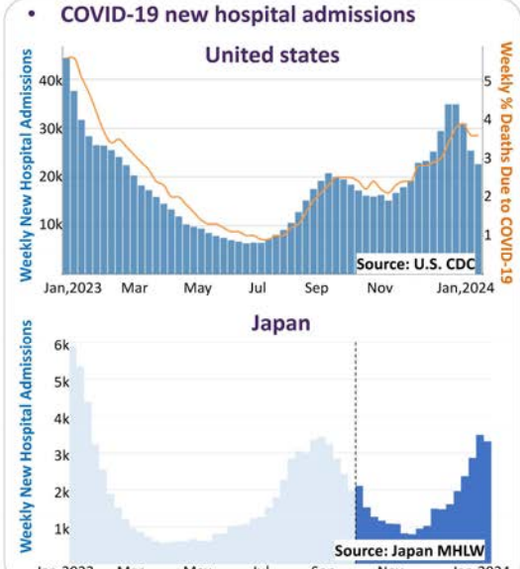
Chang-Yuil Kang, Ph.D.
Cellid Co., Ltd.

Prolonged COVID-19 Pandemic

- COVID-19 Wastewater Viral Level



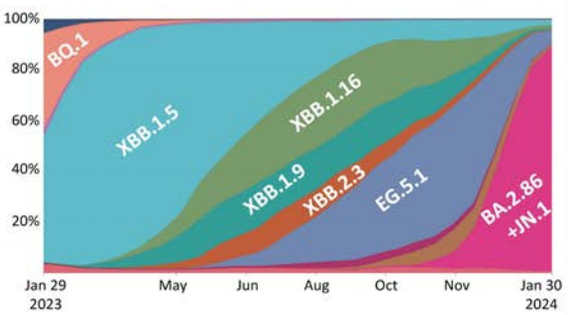
- COVID-19 new hospital admissions



2

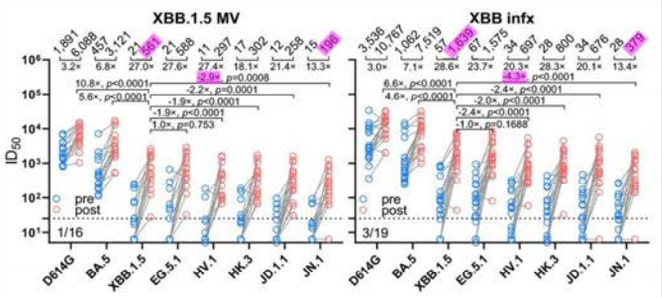
Limitations of Current Vaccines

- **Evolution of SARS-CoV-2 Variants (2023-2024, United States)**



Source: Our World In Data

- **Immune evasion of novel COVID-19 variants**



WT monovalent x 4 dose + BA.5 bivalent + XBB.1.5 monovalent mRNA vaccine

WT monovalent x 4 dose + BA.5 bivalent + XBB.1.5 infection

Wang et al., bioRxiv, 2023

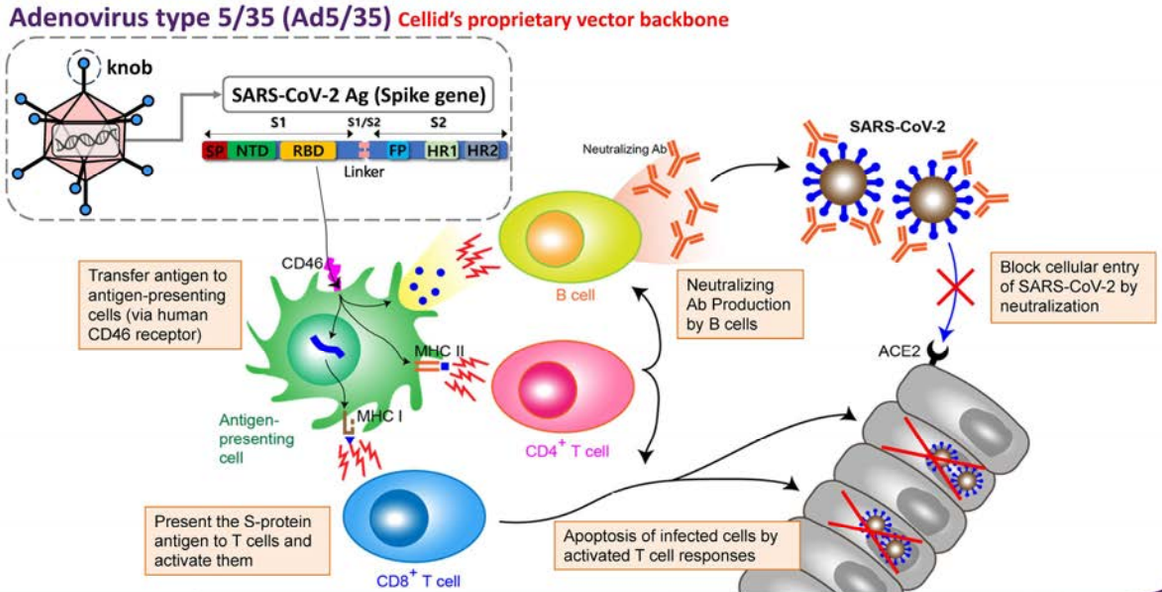
Emerging variants such as JN.1 may reduce the efficacy of current vaccines.

→ New vaccine development strategy that can defend against emerging variants is essential.

3

CELLID's COVID-19 vaccine platform

Adenovirus type 5/35 (Ad5/35) Cellid's proprietary vector backbone



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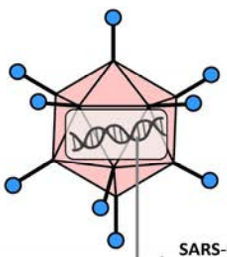
CELLID's COVID-19 vaccine platform : Competitiveness

AdCLD-CoV19-1

AdCLD-CoV19-1 OMI



01 Long-term efficacy
- Induction of neutralizing Ab and T cell immune response

02 Competitive cost
- Available at a lower cost compared to other vaccines such as mRNA vaccine
- Suitable for middle to low-income countries

03 Convenient storage and distribution
- Stored and distributed at 4 ℃
- Cold-chain system not required

04 Fast development and manufacturing process
- Rapid response to COVID-19 variants or emerging threats

5

CELLID's COVID-19 Vaccine: Current Clinical Trials

Pipeline	Antigen gene	Basic Research	Preclinical	Phase of Clinical trial			Remarks
				Phase 1	Phase 2	Phase 3	
AdCLD-CoV19	SARS-CoV-2 Spike						Primary vaccine (Discontinued due to limitations in recruiting clinical trial subjects)
AdCLD-CoV19-1 (Improved vaccine for mass manufacturing)	SARS-CoV-2 Spike						
AdCLD-CoV19-1 OMI (Omicron variant Vaccine)	SARS-CoV-2 B.1.1.529 Spike						Booster dose Vaccine (Currently in Phase 3 clinical trials Administration start date: Nov 2023.)

Developed AdCLD-CoV19-1 OMI, a vaccine against Omicron variant using a replication-deficient recombinant adenovirus serotype 5/35 platform, currently in Phase 3 clinical trials and scheduled to complete the enrollment until April 2024.

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Response to variants: Variant Vaccine Library

- Table 1. Variant-specific vaccine library

Variant	Vaccine Plasmid	Immunogenicity study	Variant	Vaccine Plasmid	Immunogenicity study
Wild type	Completed	Completed	XBB.1.5.1	Completed	Standby
Beta	Completed	Completed	XBB.1.16	Completed	Standby
Gamma	Completed	Completed	XBB.2.3	Completed	Completed
Delta	Completed	Completed	FD.2	Completed	Standby
Lambda	Completed	Completed	EG.1	Completed	Standby
Mu	Completed	Completed	XBB.1.5.10	Completed	Standby
BA.1	Completed	Completed	XBB.1.16.1	Completed	Standby
BA.2	Completed	Completed	EG.5	Completed	Standby
BA.2.12.1	Completed	Completed	XBB.1.5.68	Completed	Standby
BA.4.1	Completed	Completed	XBC	Completed	Standby
BA.5	Completed	Completed	XBC.1.6	Completed	Standby
BA.2.75	Completed	Completed	EU.1.1	Completed	Standby
BA.4.6	Completed	Standby	EG.5.1	Completed	Completed
BA.2.75.2	Completed	Standby	XBB.1.16.6	Completed	Standby
BF.7	Completed	Standby	FL.1.5.1	Completed	Standby
BQ.1	Completed	Standby	BA.2.86	Completed	Completed
BQ.1.1	Completed	Completed	JN.1	Completed	Completed
XBB	Completed	Completed	HK.3	Completed	Standby
BN.1	Completed	Completed	DV.7.1	Completed	Standby
BA.2.3.20	Completed	Standby	HV.1	Completed	Standby
XBB.1.5	Completed	Completed	HF.1	Completed	Standby
BA.2.3.20	Completed	Standby	GK.1.1	Completed	Standby
CH.1.1.1	Completed	Standby	JD.1.1	Completed	Standby
XBF	Completed	Standby	XCU	Completed	Standby

- Table 2. Pseudovirus library for neutralization test

Variants	Pseudovirus	Manufacturing	Evaluation
-	Wild type	Completed	Completed
Common	B.1.1.7/B.1.351/P.1/ B.1.617.2	Completed	Completed
α/β/γ common	B.1.1.7/B.1.351/P.1	Completed	Completed
β/γ common	B.1.351/P.1	Completed	Completed
Beta (partial)	B.1.351 (Partial)	Completed	Completed
Delta (partial)	B.1.617.1 (Partial)	Completed	Completed
Delta (partial)	B.1.617.2 (Partial)	Completed	Completed
Alpha	B.1.1.7	Completed	Completed
Beta	B.1.351	Completed	Completed
Gamma	P.1	Completed	Completed
Delta	B.1.617.2	Completed	Completed
Delta plus (Delta subtype)	AY.1 AY.4 AY.4.2 AY.43 AY.69	Completed	Completed
Lambda	C.37	Completed	Completed
Mu	B.1.621	Completed	Completed
IHU	B.1.640.2	Completed	Completed
Omicron	B.1.1.529	Completed	Completed
Stealth Omicron	BA.2	Completed	Completed
	BA.2.12.1	Completed	Completed
	BA.4.1	Completed	Completed
	BA.4/BA.5	Completed	Completed
	BA.2.75	Completed	Completed
Omicron subvariant	BA.4.6	Completed	Completed
	BA.2.75.2	Completed	Completed
	BF.7	Completed	Completed
	BQ.1	Completed	Completed
	BQ.1.1	Completed	Completed

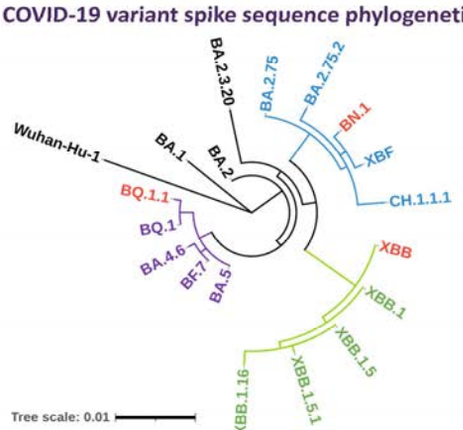
Variants	Pseudovirus	Manufacturing	Evaluation
Omicron subvariant	BN.1	Completed	Completed
	XBB	Completed	Completed
	XBB.1	Completed	Completed
	XBB.1.5	Completed	Completed
	BA.2.3.20	Completed	Completed
	CH.1.1.1	Completed	Completed
	XBF	Completed	Completed
	XBB.1.5.1	Completed	Completed
	XBB.1.16	Completed	Completed
	XBB.2.3	Completed	Completed
	FD.2	Completed	Completed
	EG.1	Completed	Completed
	XBB.1.5.10	Completed	Standby
	XBB.1.16.1	Completed	Standby
	XBC	Completed	Standby
	XBC.1.6	Completed	Completed
	EG.5.1	Completed	Completed
	EU.1.1	Completed	Standby
	FL.1.5.1	Completed	Completed
	EG.5	Completed	Standby
	XBB.1.16.6	Completed	Standby
	XBB.1.5.68	Completed	Standby
	BA.2.86	Completed	Completed
	HK.3	Completed	Completed
	DV.7.1	Completed	Standby
	HV.1	Completed	Completed
	HF.1	Completed	Ongoing
	JN.1	Completed	Completed
	GK.1.1	Ongoing	Ongoing
	JD.1.1	Ongoing	Ongoing
	XCU	Ongoing	Ongoing

- Ad5/35 platform can be easily modified to respond variants by replacing antigen to that of VOCs.

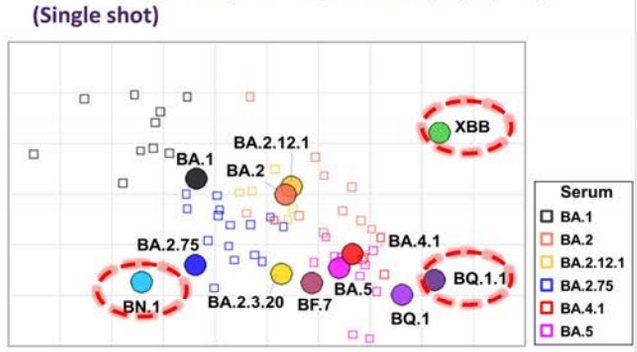
7

Clustering based on the variant sequence and the immunogenicity of the vaccine

- COVID-19 variant spike sequence phylogenetic tree



- COVID-19 variant spike antigenic cartography map (Single shot)



1 grid = two-fold serum dilution of the neutralization titer

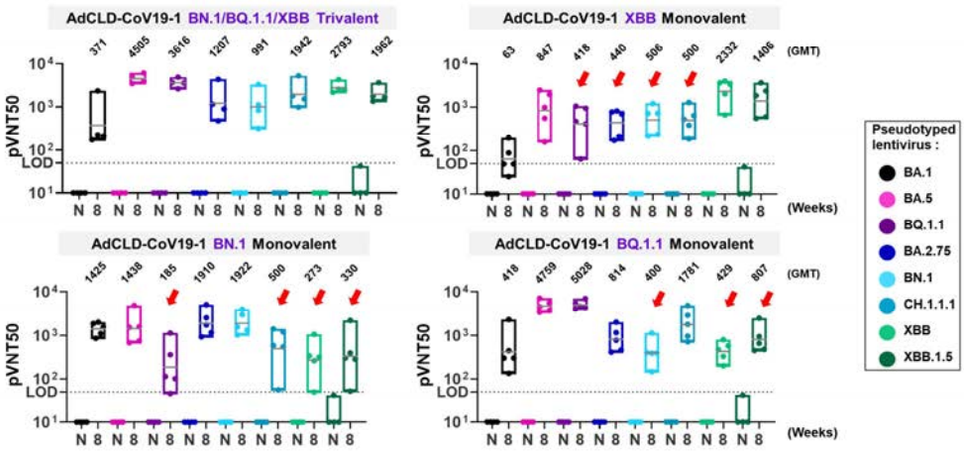
- Through the variant sequence and antigenic cartography map-based clustering produced by cross-neutralization activity, we selected **XBB, BN.1, and BQ1.1 trivalent vaccines as the candidate for the multivalent vaccine.**

Chang et al., 2024, Proc Natl Acad Sci U S A. (in press)

8

Next-generation COVID-19 vaccine development strategy: Multivalent Vaccine

- Immunogenicity of Omicron subvariant vaccines after single administration



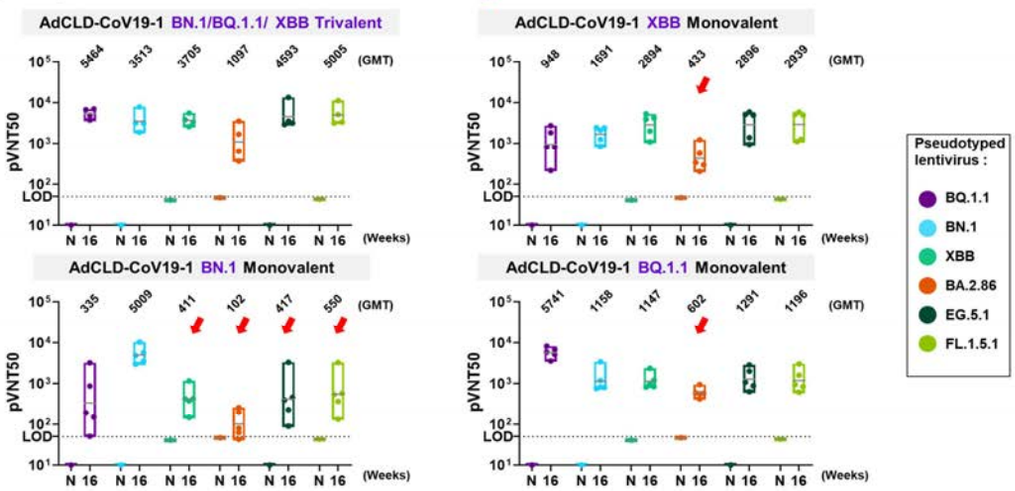
- AdCLD-CoV19-1 XBB/BN.1/BQ.1.1 trivalent vaccine enhanced cross-neutralizing activities.

Chang et al., 2024, Proc Natl Acad Sci U S A. (in press)

9

Next-generation COVID-19 vaccine development strategy: Multivalent Vaccine

- Immunogenicity of Omicron subvariant vaccines after single administration



- AdCLD-CoV19-1 XBB/BN.1/BQ.1.1 trivalent vaccine enhanced cross-neutralizing activities.

Chang et al., 2024, Proc Natl Acad Sci U S A. (in press)

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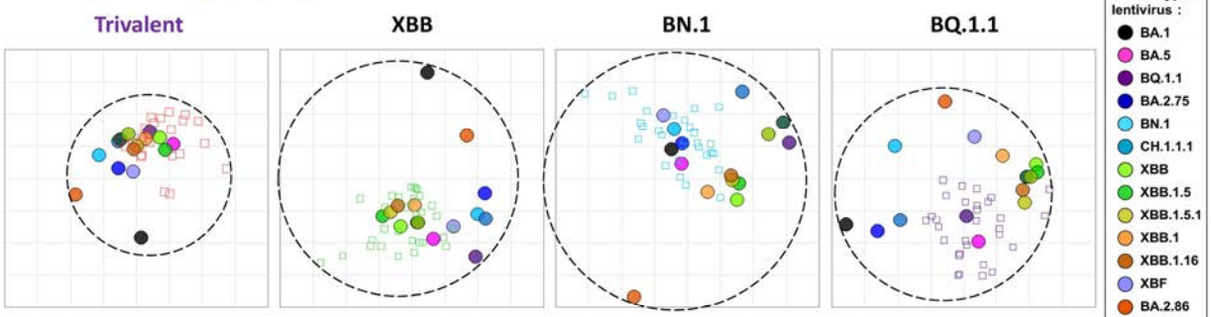
Next-generation COVID-19 vaccine development strategy: Multivalent Vaccine

- Antigenic cartography map



1 grid = two-fold serum dilution of the neutralization titer

- Average Antigenic distance in antigenic map

	Trivalent	XBB	BN.1	BQ.1.1
Variant-Variant	1.6	2.4	2.3	3.2
Serum-Variant	1.2	1.6	1.9	2.4

- By XBB/BN.1/BQ1.1 trivalent vaccine, a wide range of neutralizing antibodies was produced, and antigenic distance was reduced.

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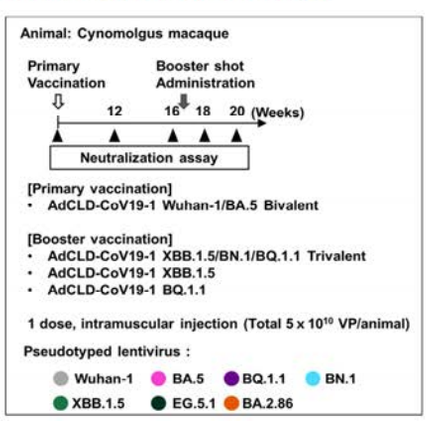
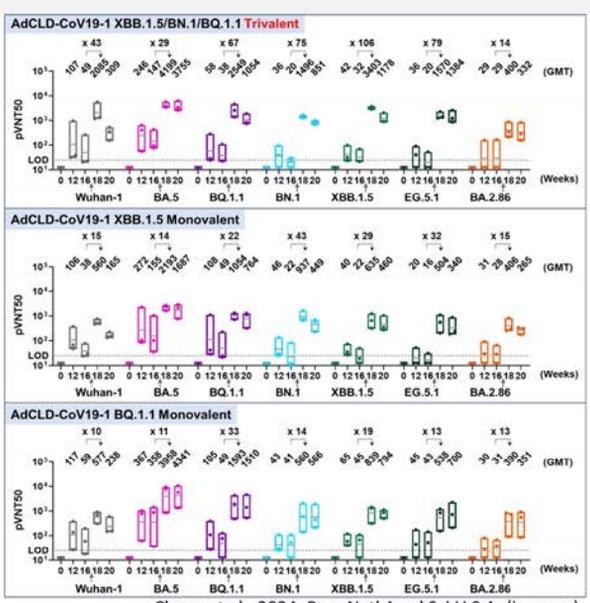
Trivalent(XBB.1.5/BN.1/BQ1.1) booster vaccine in non-human primates

- Immunogenicity of Omicron subvariant vaccines as a booster in Cynomolgus macaque



- By XBB.1.5/BN.1/BQ1.1 trivalent vaccine as a booster, a wide range of neutralizing antibodies was produced.



Chang et al., 2024, Proc Natl Acad Sci U S A. (in press)

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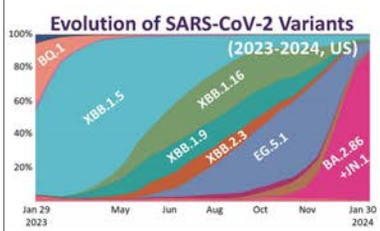
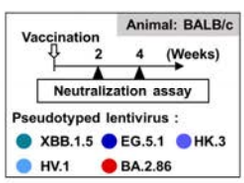
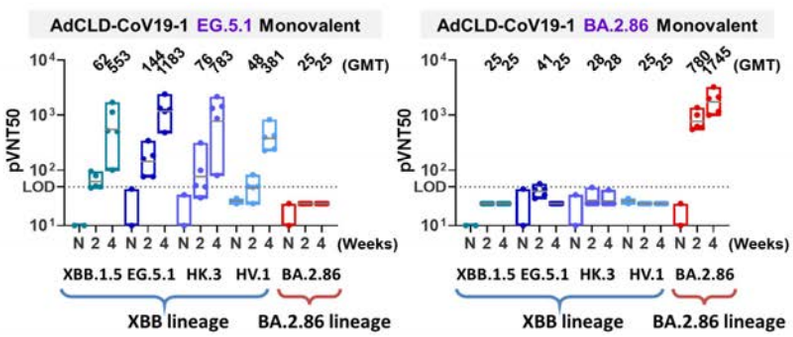
Updated Vaccine to Response Emerging Variants





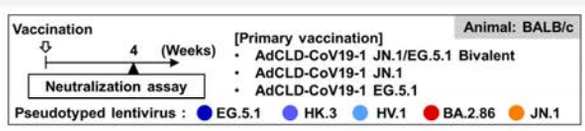
- Immunogenicity of Omicron subvariant vaccines after single administration

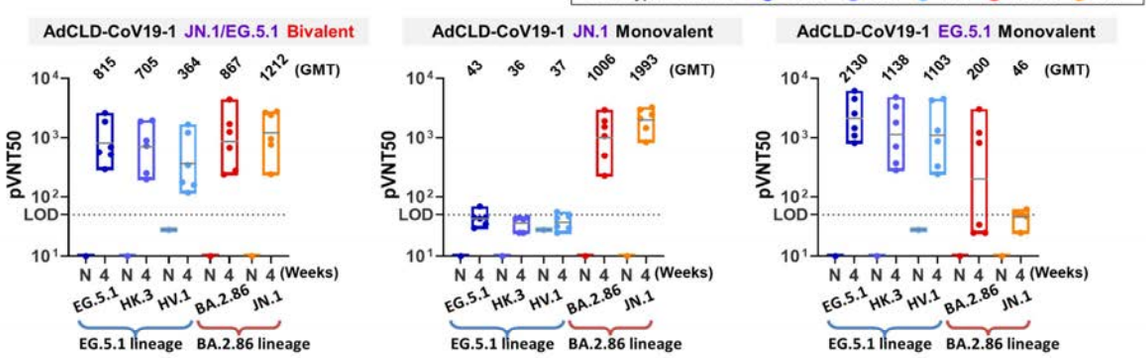


- EG.5.1 and BA.2.86 vaccines exhibit reduced cross-neutralization ability against each other.

Updated Multivalent Vaccine - Bivalent(JN.1/EG.5.1) vaccine

- Immunogenicity of Omicron subvariant vaccines after single administration





- AdCLD-CoV19-1 JN.1/EG.5.1 bivalent vaccine enhanced cross-neutralizing activities.

Summary

- The phase III clinical study of AdCLD-CoV19-1 OMI (BA.1) is currently ongoing.
- Ad5/35 platform can be easily modified to respond to variants by replacing the antigen with that of VOCs.
- We found that the trivalent vaccines could efficiently produce broadly neutralizing antibodies against most variants with a single administration and reduced antigenic distance compared to the monovalent vaccine.
- We found that EG.5.1 and JN.1 vaccines exhibit reduced cross-neutralization ability against each other. To enhance the cross-neutralizing activities to a wide range of variants, JN.1/EG.5.1 bivalent vaccines are needed.
- Ongoing efforts in vaccine development are crucial to address the challenges posed by currently circulating variants.

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LEADER IN CELL-BASED THERAPEUTIC VACCINE

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