VIRUS RESEARCH FORUM
바이러스 연구 포럼

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ibs 기초과학연구원 KVRI 한국바이러스기초연구소 바이러스연구협력협의체 과학기술정보통신부

Program

DAY 1

7월 5일 화요일

TIME	PROGRAM	
한국바이러스기초연구소 출범 1주년 기념식		
13:30 – 13:40	**축사**	**이상민 국회의원** **오태석 과학기술정보통신부 제1차관** **노도영 기초과학연구원 원장**
13:40 – 13:50	**환영사**	**한국바이러스기초연구소 1년과 나아갈 방향** • 최영기 한국바이러스기초연구소 소장
13:50 – 14:10	**사진 촬영 및 장내 정리**	
바이러스 연구 포럼		
14:10 – 15:40	**Immune responses against viral infection** [좌장] 이준행 대한미생물학회 회장	**Vaccine development for severe fever with thrombocytopenia syndrome** • 박수형 한국과학기술원 교수
		CD8 T cell differentiation during chronic viral infection • 임세진 성균관대학교 교수
		COVID-19 mRNA vaccine-induced memory T cells: Strong preserved immune responses to Omicron • 정민경 한국바이러스기초연구소 연구위원
15:40 – 15:50	**휴식**	
15:50 – 16:30	**바이러스 연구협력 협의체 대표 연구 1** [좌장] 장희창 국립감염병연구소 소장	**The unappreciated role of viral internal proteins in the extracellular compartment** • 김두진 한국생명공학연구원 책임연구원
		Exploring the immunological mechanism of viral vaccines • 김의호 한국파스퇴르연구소 팀장
16:30 – 16:40	**휴식**	
16:40 – 17:40	**Immunosenescence and T cell responses** [좌장] 정연석 대한면역학회 학술위원장	**Age-related decline of T cell immunity to viral infections** • 김철우 고려대학교 교수
		Clinical significance of bystander T cell activation in viral infection • 신의철 한국바이러스기초연구소 바이러스면역연구센터장

Program

DAY 2

7월 6일 수요일

TIME	PROGRAM	
바이러스 연구 포럼		
10:30 – 12:10	**바이러스 연구협력 협의체 대표 연구 2** [좌장] 최영기 한국바이러스기초연구소 소장	**Immunological and pathological peculiarity of severe acute respiratory syndrome coronavirus 2 beta variant** • 안대균 한국화학연구원 책임연구원
		코로나19 포함 바이러스 감염병 극복을 위한 합성신약 개발 • 김숭현 대구경북첨단의료산업진흥재단 팀장
		The development of neutralizing human antibodies against severe acute respiratory syndrome coronavirus 2 • 정효영 오송첨단의료산업진흥재단 바이오의약평가부장
		Lessons from national-wide preclinical test for COVID-19 infection • 성제경 (재)국가마우스표현형분석사업단 단장
		Interaction prediction of Omicron variants of SARS-CoV-2 • 박대의 안전성평가연구소 책임연구원
12:10 - 13:30	**사진 촬영 및 오찬**	사이언스 갤러리 (3층)
13:30 – 14:30	**Novel technologies for viral pathogenesis** [좌장] 김영봉 대한바이러스학회 회장	**Analysis of SARS-CoV-2 pathogenesis using a reverse genetic system** • 명진종 전북대학교 교수
		Differential virus-host interaction dynamics by age-dependent manners during SFTSV infection • 장호빈 한국바이러스기초연구소 선임연구원
14:30 – 14:40	**휴식**	
14:40 – 16:10	**Vaccines and animal models for SARS-CoV-2** [좌장] 김철중 충남대학교 명예교수	**mRNA vaccines against SARS-CoV-2 Delta and Omicron variants: Immunogenicity and efficacy in mice** • 오종원 연세대학교 교수
		Novel vaccine adjuvants empowered by coded signal integration • 임용택 성균관대학교 교수
		Differential parthenogenesis of SARS-CoV-2 by age-dependent and genetic variants in animal models • 최영기 한국바이러스기초연구소 소장
16:10 – 16:20	**폐회**	
16:20 – 17:00	**한국바이러스기초연구소 투어**	

VIRUS RESEARCH FORUM
바이러스 연구 포럼

7월 5일 화요일 **DAY 1**

Session 1.

Immune responses against viral infection

CHAIR 대한미생물학회 회장 | **이준행**

Session 2.

바이러스 연구협력 협의체 대표 연구 1

CHAIR 국립감염병연구소 소장 | **장희창**

Session 3.

Immunosenescence and T cell responses

CHAIR 대한면역학회 학술위원장 | **정연석**

Session 1.

Immune responses against viral infection

CHAIR

이준행

- 대한미생물학회 회장(2022~)
- 전남대학교 의과대학 교수(1993~)
- 복합면역치료연구센터 MRC 센터장(2018~)
- 국제백신학회 상임이사(2015~)

SPEAKERS

한국과학기술원 교수 I **박수형**
Vaccine development for severe fever with thrombocytopenia syndrome

성균관대학교 교수 I **임세진**
Maintenance of progenitor exhausted CD8 T cells during persistent viral infections

한국바이러스기초연구소 연구위원 I **정민경**
COVID-19 mRNA vaccine-induced memory T cells
: Strong preserved immune responses to Omicron

Vaccine development for severe fever with thrombocytopenia syndrome

Su-Hyung Park

Graduate School of Medical Science and Engineering, KAIST, Republic of Korea

Although the incidence of severe fever with thrombocytopenia syndrome virus (SFTSV) infection has increased from its discovery with a mortality rate of 10–20%, no effective vaccines are currently available. In this study, we developed a SFTSV DNA vaccine and examined its immunogenicity and protective efficacy. Vaccine candidates induced both a neutralizing antibody response and multifunctional SFTSV-specific T cell response in mice and ferrets. When the vaccine efficacy was investigated in aged-ferrets that recapitulate fatal clinical symptoms, vaccinated ferrets were completely protected from lethal SFTSV challenge without developing any clinical signs. A serum transfer study revealed that anti-envelope antibodies play an important role in protective immunity. Our results suggest that Gn/Gc may be the most effective antigens for inducing protective immunity and non-envelope-specific T cell responses also can contribute to protection against SFTSV infection. Furthermore, we found that this DNA vaccine induced a strong neutralizing antibody and SFTSV-specific T cell response in monkeys, which was comparable with that observed in SFTS patients. This study provides important insights into the development of an effective vaccine, as well as corresponding immune parameters, to control SFTSV infection.

Maintenance of progenitor exhausted CD8 T cells during persistent viral infections

Sejin Im

School of Medicine, Sungkyunkwan University, Suwon, Republic of Korea

CD8 T cells play a pivotal role in the control of chronic viral infections and cancer. However, antigen-specific CD8 T cells persist in a dysfunctional or exhausted state characterized by upregulation of inhibitory receptors such as PD-1 and progressive loos of effector functions and proliferative capacity during chronic infection and cancer. We have recently identified a population of progenitor exhausted CD8 T cells (Tpex) which act as resource cells to maintain CD8 T cell responses during chronic viral infections. More importantly, the Tpex cells exclusively provide the proliferative burst after PD-1 pathway blockade, suggesting this CD8 T cell subset as a novel target of immunotherapies. However, the mechanisms regulating Tpex maintenance during persistent viral infection remain to be investigated. To examine whether new thymic input of naïve CD8 T cells generates the Tpex cells by the continual activation under high viral loads, we compared the kinetics of virus-specific CD8 T cells between thymectomized mice and sham controls. The population of Tpex and terminally exhausted (Ttex) CD8 T cells in thymectomized mice was comparable to that in sham controls, indicating a dispensable role of thymic input in the maintenance of Tpex cells. Instead, we found that the Tpex cells undergo self-renewal predominantly in the bone marrow of chronically infected mice. Furthermore, ex vivo treatment of IL-15 preferentially enhanced the proliferation of Tpex cells rather than Ttex cells. When we administered IL-15 to chronically infected mice, self-renewal of Tpex was significantly increased, which was more pronounced in the bone marrow, similar to memory CD8 T cells developed following acute viral infections. Taken together, these results suggest that the Tpex subset is maintained not by a supply of newly emerged Tpex cells but by self-renewal, which preferentially occurs in the bone marrow and is driven by IL-15 stimulation.

COVID-19 mRNA vaccine-induced memory T cells : Strong preserved immune responses to Omicron

Min Kyung Jung[1], Seong Dong Jeong[1],
Dong-Uk Kim[2], Sungmin Jung[2] and Eui-Cheol Shin[1,2]

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Since the first report of coronavirus disease, 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in December 2019, COVID-19 vaccines have been developed at an unprecedented pace and administered to large populations on a global scale. However, the pandemic continues due to the rapid decay of neutralizing antibodies (nAbs) and the emergence of variants, including the Omicron (B.1.1.529) variant. In the present study, we investigated whether BNT162b2 mRNA vaccine-induced memory T cells functionally respond to the Omicron spike. Experiments were performed using samples from healthcare workers (HCWs) who were immunized with two or three doses of the BNT162b2 mRNA vaccine, and individuals with prior SARS-CoV-2 infection who were immunized with two doses of BNT162b2. Vaccine-induced memory T cells exhibited substantial responses to the Omicron spike, with no difference between HCWs with two versus three vaccine doses. In individuals with prior infection, two-dose vaccination robustly boosted memory T cells that responded to the Omicron spike as well as the Wuhan-Hu-1 spike. Importantly, polyfunctionality was preserved in vaccine-induced memory T cells responding to the Omicron spike. The present findings indicate that BNT162b2-induced memory T cells substantially respond to the Omicron variant with preserved polyfunctionality. These findings suggest that memory T cells will exert effector functions against the Omicron variant during breakthrough infections among individuals immunized with COVID-19 vaccines.

Session 2.

바이러스 연구협력 협의체 대표 연구 1

CHAIR

장희창

- 국립감염병연구소 소장(2020~)
- 전남대학교 의과대학 교수(2018~)
- 질병관리청 기관윤리심의위원회 위원장(2021~)

SPEAKERS

한국생명공학연구원 책임연구원 | **김두진**
The unappreciated role of viral internal proteins in the extracellular compartment

한국파스퇴르연구소 팀장 | **김의호**
Exploring the immunological mechanism of viral vaccines

The unappreciated role of viral internal proteins in the extracellular compartment: Extracellular nucleoprotein exacerbates influenza virus pathogenesis by activating Toll-like receptor 4 and the NLRP3 inflammasome

Chang-Ung Kim[1,2], Yu-Jin Jeong[3], Pureum Lee[3,4], Moo-Seung Lee[3,4],
Jong-Hwan Park[5], Young-Sang Kim[2,*], Doo-Jin Kim[1,2,4*]

[1] Infectious Disease Research Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon, Republic of Korea
[2] Department of Biochemistry, Chungnam National University, Daejeon, Republic of Korea
[3] Environmental Diseases Research Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon, Republic of Korea
[4] University of Science and Technology (UST), Daejeon, Republic of Korea
[5] College of Veterinary Medicine, Chonnam National University, Gwangju, Republic of Korea

Host immune responses, such as those initiated by pattern recognition receptor (PRR) activation, are important for viral clearance and pathogenesis. However, little is known about the interactions of viral proteins with surface PRRs or, more importantly, the association of innate immune activation with viral pathogenesis. In this study, we showed that internal influenza virus proteins were released from infected cells. Among these proteins, nucleoprotein (NP) played a critical role in viral pathogenesis by stimulating neighboring cells through toll-like receptor (TLR)2, TLR4, and the NLR family pyrin domain containing 3 (NLRP3) inflammasome. Through the activation of these PRRs, NP induced the production of interleukin (IL)-1β and IL-6, which subsequently led to the induction of trypsin. Trypsin induced by NP increased the infectivity of influenza virus, leading to increases in viral replication and pathology upon subsequent viral infection. These results reveal the role of released NP in influenza pathogenesis and highlight the importance of the interactions of internal viral proteins with PRRs in the extracellular compartment during viral pathogenesis.

Keywords: Influenza virus; Nucleoprotein; Toll-like receptor; Cytokine-trypsin cycle

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Exploring the immunological mechanism of viral vaccines

Euiho Kim

Institut Pasteur Korea, Seongnam, Republic of Korea

Vaccines have been the most successful medical intervention to prevent infectious diseases in history. Recent advances in vaccinology enabled the invention of safe subunit vaccines, followed by record-breaking development of gene-based COVID-19 vaccines. However, a crucial question on how these different vaccine platforms trigger and modulate the immunogenicity and longevity of immune response requires further investigation. Vaccine adjuvant is often required for enhancing immunogenicity of subunit or inactivated vaccines. Particularly, emulsion vaccine adjuvant has been utilized in influenza vaccine and COVID-19 vaccine to induce protective immunity. Our recent study demonstrates the important role of cell death & DAMP pathway in antibody and T cell responses upon the emulsion-adjuvanted vaccination. In addition, recent data on the induction and maintenance of vaccine-mediated immunity by COVID-19 mRNA or viral vector vaccines will be briefly shared.

Session 3.

Immunosenescence and T cell responses

CHAIR

정연석

- 대한면역학회 학술위원장(2022~)
- 서울대학교 약학대학 교수(2014~)
- The University of Texas-Medical School 부교수(2010~)

SPEAKERS

고려대학교 교수 | **김철우**
Age-related decline of T cell immunity to viral infections

한국바이러스기초연구소 바이러스면역연구센터장 | **신의철**
Clinical significance of bystander T cell activation in viral infection

Age-related decline of T cell immunity to viral infections

Chulwoo Kim

Department of Microbiology, College of Medicine, Korea University, Seoul, Republic of Korea

Generation of protective T cell responses declines with age, leading to increased susceptibility to infections such as with SARS-CoV-2 virus. Studies have examined age-associated changes in microRNA networks causing this defect. Increased miR-21 expression in aged naïve T cells results in sustained activation of multiple signaling pathways, which favors the differentiation of hyper-inflammatory effector cells over memory precursor cells after T cell activation. Another example is the reduced expression of miR-181a in naïve T cells from older individuals. We show that miR-181ab1 deficiency in peripheral murine T cells causes defective T cell expansion and delayed viral clearance after acute infection, resembling human immune aging. Naïve T cells from older individuals as well as miR-181ab1-deficient murine T cells develop excessive replication stress after activation, due to reduced histone expression and delayed S-phase cell cycle progression. Reduced histone expression is caused by the miR-181a target SIRT1. Inhibition of SIRT1 activity increases histone expression and diminishes replication stress in replicating T cells from old individuals. Correspondingly, treatment with SIRT1 inhibitors improves viral clearance in miR-181a-deficient mice after infection. Therefore, SIRT1 inhibition may be beneficial to treat systemic viral infection in older individuals.

Clinical significance of bystander T cell activation in viral infection

Eui-Cheol Shin

The Center for Viral Immunology, Korea Virus Research Institute,
Institute for Basic Science (IBS), Daejeon, Republic of Korea, and
Graduate School of Medical Science and Engineering, KAIST, Daejeon, Republic of Korea

During viral infection, pre-existing memory CD8+ T cells that are not specific for the infecting virus can be activated by cytokines without cognate antigens, termed bystander activation. Recent studies have demonstrated that bystander-activated CD8+ T cells exert either protective or detrimental effects on the host depending on the infection model or disease. In this lecture, I will present our recent data showing the mechanisms and immunopathological roles of IL-15-induced bystander CD8+ T cell activation in acute viral hepatitis. In addition, I will discuss molecular regulations of bystander activation-related genes and clinical significance of bystander activation.

VIRUS RESEARCH FORUM
바이러스 연구 포럼

7월 6일 수요일 DAY 2

Session 4.
바이러스 연구협력 협의체 대표 연구 2

CHAIR 한국바이러스기초연구소 소장 | **최영기**

Session 5.
Novel technologies for viral pathogenesis

CHAIR 대한바이러스학회 회장 | **김영봉**

Session 6.
Vaccines and animal models for SARS-CoV-2

CHAIR 충남대학교 명예교수 | **김철중**

Session 4.

바이러스 연구협력 협의체 대표 연구 2

CHAIR

최영기

- 기초과학연구원 한국바이러스기초연구소 소장(2021~)
- 충북대학교 의과대학 교수(2004~)
- The Journal of Microbiology 에디터(2016~)

SPEAKERS

한국화학연구원 책임연구원 I **안대균**
Immunological and pathological peculiarity
of severe acute respiratory syndrome coronavirus 2 beta variant

대구경북첨단의료산업진흥재단 팀장 I **김승현**
코로나19포함 바이러스 감염병 극복을 위한 합성신약 개발

오송첨단의료산업진흥재단 바이오의약평가부장 I **정효영**
The development of neutralizing human antibodies
against severe acute respiratory syndrome coronavirus 2

(재)국가마우스표현형분석사업단 단장 I **성제경**
Lessons from national-wide preclinical test for COVID-19 infection

안전성평가연구소 책임연구원 I **박대의**
Interaction prediction of Omicron variants of SARS-CoV-2

Immunological and pathological peculiarity of severe acute respiratory syndrome coronavirus 2 beta variant

Dae-Gyun Ahn

Center for Convergent Research of Emerging Virus Infection, Korea Research Institute of Chemical Technology,
Daejeon, Republic of Korea

Diverse severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have emerged since the beginning of COVID-19 pandemic. We investigated the immunological and pathological peculiarity of SARS-CoV-2 beta variant of concern (VOC) compared to the ancestral strain. Comparative analysis of phenotype and pathology revealed that the beta VOC induces slower disease progression and prolonged presymptomatic period in the early stages of SARS-CoV-2 infection, but ultimately causes sudden death in the late stages of infection in the K18-hACE2 mouse model. The beta VOC induced enhanced activation of CXCL1/2– CXCR2–NLRP3–IL-1β signal cascade accelerating neutrophil recruitment and lung pathology in beta variant-infected mice, as evidenced by multiple analyses of SARS-CoV-2-induced inflammatory cytokine and transcriptome. This presentation will discuss the recent findings of the variant characteristics for a better understanding of SARS-CoV-2 pathogenesis and need for treatment.

코로나19 포함 바이러스 감염병 극복을 위한 합성신약 개발

김 숭 현

대구경북첨단의료산업진흥재단 신약개발지원센터 감염성질환팀장

SARS-CoV-2 바이러스 유래의 코로나19 감염병에 의해 사회/경제적 위기가 전 세계적으로 지속되고 있음. 발병 초기 글로벌 팬데믹에 대한 신속한 대응을 위해 약물재창출 방법으로 치료제가 제시되었으나, 렘데시비르 건에서 볼 수 있듯이, 코로나19에 대한 약효가 불확실하였고 적지 않은 부작용들이 나타남. 이 후, 혁신적인 백신기술의 개발로 코로나19의 치사율도 낮아지고 어느 정도 진정세로 돌입하고 있지만, 코로나19의 종식과 향 후 발병 가능한 바이러스 감염병에 대한 대책 마련을 위해서도 SARS-CoV-2 바이러스 자체에 대해 최적화된 약물이 개발될 필요성이 있음.

이러한 약물의 개발을 위해서는 SARS-CoV-2 바이러스의 구조와 인간세포에서의 복제주기, 복제 후 면역작용에 대한 자세한 이해를 필요로 함. 또한, 현재 대두되고 있는 코로나19 변이와 향 후 발병 가능한 다른 바이러스 감염병에 대한 대처를 위해서도 약물 개발을 위한 타겟의 선정이 중요하다고 할 수 있음. 제대로 된 약물의 개발을 위해서는 타겟 분석, 화합물의 디자인/합성, 약효/약물성/동물효능/독성 평가 등 신약개발 후보물질 발굴에 필요한 일련의 과정들이 유기적으로 잘 접목되어야 함. 특히, 이러한 화합물의 프로파일들은 초기 디자인에서 대부분 결정이 난다고 해도 과언이 아니기 때문에, 분자 설계와 의약화학의 역할이 그만큼 중요하다고 할 수 있음. 본 세미나에서는 현재 개발된 코로나19 치료제들과 비교하여 신약센터에서 개발하고 있는 바이러스 타겟들 각각에 대한 합성 화합물들의 연구결과들에 대해서 논의하고자 함.

The development of neutralizing human antibodies against severe acute respiratory syndrome coronavirus 2

Chung Hyo-Young

New Drug Development Center, Osong Medical Innovation Foundation, Cheongju, Chungbuk, Republic of Korea

Since it was first reported in Wuhan, China, in 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic outbreak resulting in a tremendous global threat due to its unprecedented rapid spread and an absence of a prophylactic vaccine or therapeutic drugs treating the virus. The receptor-binding domain (RBD) of the SARS-CoV-2 spike protein is a key player in the viral entry into cells through its interaction with the angiotensin-converting enzyme 2 (ACE2) receptor protein, and the RBD has therefore been crucial as a drug target. In this study, we used phage display to develop human monoclonal antibodies (mAbs) that neutralize SARS-CoV-2. A human synthetic Fab phage display library was panned against the RBD of the SARS-CoV-2 spike protein (SARS-2 RBD), yielding ten unique Fabs with moderate apparent affinities (EC50 = 19-663 nM) for the SARS-2 RBD. All of the Fabs showed no cross-reactivity to the MERS-CoV spike protein, while three Fabs cross-reacted with the SARS-CoV spike protein. Five Fabs showed neutralizing activities in in vitro assays based on the Fabs' activities antagonizing the interaction between the SARS-2 RBD and ACE2. Reformatting the five Fabs into immunoglobulin Gs (IgGs) greatly increased their apparent affinities (KD = 0.08-1.0 nM), presumably due to the effects of avidity, without compromising their non-aggregating properties and thermal stability. Furthermore, two of the mAbs (D12 and C2) significantly showed neutralizing activities on pseudo-typed and authentic SARS-CoV-2. Given their desirable properties and neutralizing activities, we anticipate that these human anti-SARS-CoV-2 mAbs would be suitable reagents to be further developed as antibody therapeutics to treat COVID-19, as well as for diagnostics and research tools.

Lessons from national-wide preclinical test for COVID-19 infection

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COVID-19 has spread worldwide, causing significant morbidity and mortality. Throughout the recent pandemic, South Korea led national efforts to develop vaccines and therapeutics to treat and prevent SARS-CoV-2 using Korean national research funding. The project proceeded as follows: 1) evaluation system setup (including Animal Biosafety Level 3 (ABSL3) facility alliance, standardized nonclinical evaluation protocol, application website, and COVID-19-specific laboratory information management system), 2) application (including application, committee review, and candidate selection), and 3) evaluation (including nonclinical efficacy study, data analysis, expert judgment, and reporting). After receiving 101 applications, the selection committee reviewed pharmacokinetics, toxicity, and efficacy data associated with the mechanism of action (MOA) and selected 32 final candidates. In the nonclinical efficacy test, we used golden Syrian hamsters and human angiotensin-converting enzyme 2 transgenic mice under a cytokeratin 18 promoter to evaluate mortality, clinical signs, body weight, viral titer, neutralizing antibody presence, and histopathology. The comprehensive data indicated eight new drug candidates and one repositioned drug, which demonstrated significant efficacy in preventing or treating COVID-19. Three vaccine and four antiviral drug candidates exerted significant protective activities according to various parameters related to SARS-CoV-2 pathogenesis. Additionally, two anti-inflammatory drug candidates showed therapeutic effects on lung lesions and weight loss through their characteristic MOA but did not affect viral replication. Along with systematic verification of applicability of representative COVID-19 animal models through large-scale nonclinical studies, our findings suggest that ABSL3 multicenter alliance and nonclinical evaluation protocol standardization can promote rapid and reliable efficacy testing against COVID-19, thus expediting medical product development.

Keywords: SARS-CoV-2; COVID-19; Nonclinical; hACE2 mouse; Golden Syrian hamster.

Interaction prediction of Omicron variants of SARS-CoV-2

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In the past 2 years, since the emergence of severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), multiple SARS-CoV-2 variants have emerged. Whenever a new variant emerges, considerable time is required to analyze the binding affinity of the viral surface proteins to human angiotensin-converting enzyme 2 (hACE2) and monoclonal antibodies. To efficiently predict the binding affinities associated with hACE2 and monoclonal antibodies in a short time, herein, we propose a method applying statistical analysis to simulations performed using molecular and quantum mechanics. This method efficiently predicted the trend of binding affinity for the binding of the spike protein of each variant of SARS-CoV-2 to hACE2 and individually to eight commercial monoclonal antibodies. Additionally, this method accurately predicted interaction energy changes in the crystal structure for 10 of 13 mutated residues in Omicron variant, showing a significant change in the interaction energy of hACE2. S375F was found to be a mutation that majorly changed the binding affinity of the spike protein to hACE2 and the eight monoclonal antibodies. Our proposed analysis method enables the prediction of the binding affinity of new variants to hACE2 or to monoclonal antibodies in a shorter time compared to that utilized by the experimental method.

Session 5.

Novel technologies for viral pathogenesis

CHAIR

김영봉

- 대한바이러스학회 회장(2022~)
- 건국대학교 의생명공학과 교수(2003~)
- KR BIOTECH 대표이사(2009~)

SPEAKERS

전북대학교 교수 I **명진종**
Analysis of SARS-CoV-2 pathogenesis using a reverse genetic system

한국바이러스기초연구소 선임연구원 I **장호빈**
Differential virus-host interaction dynamics
by age-dependent manners during SFTSV infection

Analysis of SARS-CoV-2 pathogenesis using a reverse genetic system (NSP1: A major virulence factor of SARS-CoV-2)

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The first SARS-CoV-2 infection case is believed to occur on December 1, 2019, and was reported to the WHO on December 31, 2019. The failure of China's prompted actions, combined with the nature of high viral infectivity, resulted in the COVID pandemic, with over 6.3 million deaths and 530 million infection cases as of June 6, 2022. During the early stages of the pandemic, the focus of research was on the development of vaccines and therapeutics. The tide is now slowly turning toward understanding the molecular mechanisms of SARS-CoV-2-mediated pathogenesis. The coronavirus non-structural protein 1 (NSP1) is known to be a major virulence factor. We show that NSP1 of SARS-CoV-2 strongly inhibited MDA5-mediated activation of interferon beta promoter activities via protein downregulation. MDA5 mRNA was protected with the stem-and-loop 1 (SL1) of the 5'UTR of the SARS-CoV-2 genome, and NSP1-mediated inhibition of IFN signaling was restored, indicating that the NSP1-mediated suppression was nullified in the presence of SL1, which highlights the importance of NSP1 in the immune evasion. NSP1 also strongly inhibits TBK1 and IRF3-mediated IFN induction activation. Furthermore, NSP1 appears to interfere with IRF3 phosphorylation, which may result in impaired nuclear translocation and subsequent transcriptional activation. Currently, we have successfully generated NSP1 deficient mutant viruses and are investigating the functions of these viruses.

Differential virus-host interaction dynamics by age-dependent manners during SFTSV infection

Ho bin Jang

Korea Virus Research Institute, Institute of Basic Science

Severe fever with thrombocytopenia syndrome (SFTS), caused by a novel phlebovirus, a type of virus transmitted by arthropod vectors, particularly ticks, is a growing global health concern. SFTS shows an average of ~30% fatality rate, manifesting multi-systemic organ failure. Although recent studies reported that the severity of SFTS is closely associated with age, however, the underlying mechanism remains elusive due to the poor accessibility of clinical samples. Therefore, to better understand the age-associated infection dynamics of SFTSV, we used a ferret animal model which was previously demonstrated to be susceptible to SFTSV, exhibiting clinical manifestation of the disease including high mortality. In this study, young and aged ferrets were infected with SFTSV, from which, multiple tissue samples including spleen, bone marrow (BM), and peripheral blood mononuclear cells (PBMC) were collected at different time points over the infection period. Subsequently, results of the single-cell RNA sequencing and computational analyses of ~440,000 cells from a total of 72 tissue samples revealed differential SFTSV infection patterns and cell population changes in an age-dependent manner. Notably, in terms of absolute number and % fraction of cell populations, cells with SFTSV viral read(s) (e.g., SFTSV (+) cells) of the aged ferrets drastically increased and continued to expand to other cell types across all tissues at 6 days post-infection (dpi) following the first detection at 2 dpi. While in young ferrets, the SFTSV (+) cells decreased after a peak at 4 dpi (spleen) and were barely detected over 6 dpi (BM and PBMC), hence, possibly indicating the association of age with viral clearance. Further, we found such aberrant expansion of viral (+) cells mainly occurred in proliferative B cell-lineages, expressing S-G2-M phase genes. Although there are still many unknowns from this large-scaled data, our efforts here represent an essential first step in understanding the host-virus interaction dynamics in an age-dependent manner during SFTSV infections in vivo model. More in-depth and targeted analyses are actively underway to find critical factor(s) impacting the age-dependence of SFTS severity.

Session 6.

Vaccines and animal models for SARS-CoV-2

CHAIR

김철중

- 충남대학교 수의과대학 명예교수(2021~)
- IBS 한국바이러스기초연구소 방문석학(2021~)

SPEAKERS

연세대학교 교수 I **오종원**
mRNA vaccines against SARS-CoV-2 Delta and Omicron variants:
Immunogenicity and efficacy in mice

성균관대학교 교수 I **임용택**
Novel vaccine adjuvants empowered by coded signal integration

한국바이러스기초연구소 소장 I **최영기**
Differential parthenogenesis of SARS-CoV-2 by age-dependent
and genetic variants in animal models

mRNA vaccines against SARS-CoV-2 Delta and Omicron variants
: Immunogenicity and efficacy in mice

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The COVID-19 pandemic is still a public health threat. Emergence of variants limits the effectiveness of current vaccines including mRNA vaccines, which have been most rapidly and widely distributed for emergency use at an unprecedented speed. Despite its merit of rapid responding to newly emerging viruses, the current mRNA vaccine uses yet the viral spike protein (S) antigen of an early emerged S clade severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Currently, according to the viral genome sequence data sets deposited by a limited number of countries with higher vaccination rates, the Omicron (B.1.1.529) variant and its subvariants (BA.1–BA.5) are predominant along with a minor fraction of the Delta variant. These two major variants of concerns (VOCs), particularly the Omicron with a wide variability in the receptor binding domain of the S protein, are less efficiently neutralized by antibodies against the early emerged SARS-CoV-2. In addition, even the titers of these neutralizing antibodies decline within a few months after vaccination. Waning immunity along with emergence of vaccine escape mutants, therefore, would become a rising threat in most countries where second or third booster immunization had been completed early this year, and/or in places where there was a massive wave of Omicron infections. Although S antigen-specific T cells may contribute in part, in clearing less pathogenic, highly transmissible Omicron VOC, the search for more effective mRNA vaccines against multiple VOCs or a currently prevailing VOC has become more urgent. This presentation will review the current status of the COVID-19 vaccine for VOCs and platform technologies that need to be improved in the development of the second generation COVID-19 vaccine against VOCs, and will share our results from recent studies of Delta and Omicron S antigen-targeting mRNA vaccines tested in mice, with a particular focus on S antigen design and effective expression.

Novel vaccine adjuvants empowered by coded signal integration

Yong Taik Lim

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Sungkyunkwan University (SKKU), Suwon, Gyeonggi-do, Republic of Korea

In this talk, general issues in the development of vaccine adjuvants will be discussed briefly, which followed by the introduction of novel vaccine adjuvants generated by the coded signal integration of innate stimuli. Vaccine adjuvants are compounds that can increase and/or modulate the intrinsic immunogenicity of an antigen. Rationally designed adjuvants can induce potent and persistent immune responses as well as minimize immune-related toxicities. Recently, taking cues from pathogen infection, our research group has developed a novel type of immunostimulatory system which integrated innate stimuli in the context of time, order, and duration. Here, I would like to present the representative immunological characteristics of the newly developed immunostimulatory system and discuss the prospects of it as a next-generation vaccine adjuvant.

Differential parthenogenesis of SARS-CoV-2 by age-dependent and genetic variants in animal models

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To understand differing COVID-19 manifestations in patients of different ages, three age groups of ferrets were infected with SARS-CoV-2. Although SARS-CoV-2 was isolated from all ferrets regardless of age, aged ferrets (≥3 years old) showed higher viral loads, longer nasal virus shedding, and more severe lung inflammatory cell infiltration and clinical symptoms compared to juvenile (≤6 months) and young adult (1-2 years) groups. Transcriptome analysis of aged ferret lungs revealed strong enrichment of gene sets related to type I interferon, activated T cells, and M1 macrophage responses, mimicking the gene expression profile of severe COVID-19 patients. Further, given the emergence of multiple severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants globally, to understand the biological characteristics of recent SARS-CoV-2 variants, we tested nine different SARS-CoV-2 strains in Syrian hamster model for comparison of histopathological differences and viral loads in respiratory tracts and in ferret model for assessment of transmission characteristics. Syrian hamster infection demonstrated that recent alpha-, beta- and delta-SARS-CoV-2 variants had higher titers and persisted longer in the upper respiratory tract compared to their reference strains. Ferret-to-ferret transmission study demonstrated that the G, GH, GR, and recent variants exhibited rapid and long-term transmissibility. Of the nine infection groups, the beta-virus infected ferrets showed the lowest cross-relativity with other viruses and evidenced active breakthrough infection by direct contact with delta-virus infected ferrets. These data suggest that the evolutionary forced mutations of SARS-CoV-2 are associated with the virulence and transmissibility, thus a periodic evaluation of contemporary SARS-CoV-2 variants is critical to understand their pathogenic characteristics.

Keywords: COVID-19; Age-dependent; Ferrets; Pathogenesis; Clinical manifestations

Virus Research Forum

바이러스 연구 포럼

넥스트 팬데믹을 위한 바이러스 연구

Preparedness for the next pandemic