#### e-ASIA Joint Research Program Final Report

**1. Project title :** [ International study on pulmonary diseases infected with influenza virus and Mycobacterium tuberculosis ]

#### 2. Joint Research period : January 1, 2014 $\,\sim\,$ March 31, 2017

#### 3. Research Team :

Country 1 team (up to 6 people including the Principal Investigator) Japan (AMED) Funding period: January 1, 2014 – March 31, 2017 Total Funded Amount (in Local Currency):46,400,000 yen

	Name	Position	Affiliation	Role in the project
Flu team				
PI	Kazuo Suzuki	Director Professor	Asia International In stitute of Infectious Disease Control, Te ikyo University	General coordinator
Collaborator	Shoichi Suzuki	Associate Professor	Asia International In stitute of Infectious Disease Control, Te ikyo University	NS1 gene mu tation associat ed with pneu monia
Collaborator	Shoji Kawachi	Vice director	Asia International In stitute of Infectious Disease Control, Te ikyo University	Clinical trial of Josamycin
TB team			· · ·	•
Collaborator	Seiya Kato	Vice director	Research Institute of Tuberculosis (RI T), JATA	General mana gement of the project
Collaborator	Naoto Keicho	Head	Research Institute of Tuberculosis (RI T), JATA	Management of clinical stu dies
Collaborator	Shinji Maeda	Professor	Hokkaido Pharmace utical University Sc hool of Pharmacy	Genotyping an d technical tra nsfer
I otal number of participants including students:1/				

County 2 team (up to 6 people including the Principal Investigator) Vietnam (MOST) Funding period: June 2014 ~ November 2017

Role in the Name Position Affiliation project Flu team ΡI Phung Thi Bich Head of Vietnam National C General coordi hildren's Hospital Thuy departmen nator and Gen e analysis Tran Minh Dien Vice-direct Vietnam National C Collaborator General coordi hildren's Hospital nation or TB team Dr.Le Van Duc General coordi Collaborator Director Da Nang Lung Hos pital (former name: nation/supervis Da Nang hospital o ion of on-site f Tuberculosis and implementation Lung Diseases) Dr. Pham Huu Hanoi Lung Hospita Technical assi Collaborator Director Thuong stance Collaborator Dr. Nguyen Thi Program NCGM-BMH Medica Supervision of Coordinat Le Hang on-site implem I Collaboration Cent entation or er Total number of participants including students: 5

Total Funded Amount (in Local Currency): 2.650 milion VND

County 3 team (up to 6 people including the Principal Investigator) Philippines (DOST) Funding period: January 29, 2014 - December 29, 2017

Total Funded Amount (in Local Currency): Php 5,688, 659.00

	Name	Position	Affiliation	Role in the project		
TB team						
PI	Jaime C. Montoya	Professor	UP College of Medi cine	General mana ger of TB Pro ject		
Collaborator	Anna Lena Lopez	Associate Professor	National Institutes o f Health, UP Manil a	Co-Investigato r		
Flu team						
Collaborator	Dr. Marilla G. Lucero	Medical Consultant	Research Institute f or Tropical Medicin e	Leader of Flu team, sample management		
Collaborator	Dr. Salvacion R. Gatchalian	Pediatric Consultant	Philippine General Hospital	Clinical trial of Josamycin		
Collaborator	Dr. Joanne N. De Jesus	Medical Consultant	Research Institute f or Tropical Medicin e	Sample collect or		
Collaborator	Dr. Mario Ant onio L. Jiz	Head, Immunolo gy Lab.	Research Institute f or Tropical Medicin e	Analysis of cy tokines		
Total number of participants including students:70						

#### 4. Summary of the joint research

#### Flu team

Japan

We analyzed a role of Non-structural protein 1 (NS1) for severe pneumoniae induction using modeling simulation in gene mutation in influenza virus. Mutation at 42th amino acid which has RNA binding domain shows a virulence of H5N1 with cytokine storm (Kato *et al.* 2016). This study was performed by all project members and PhD students Ms. Nguyen T. and Dr. Tran H.D. supported by MEXT-Monka-sho in Japan. <u>Clinical trial to evaluate the effect of Leucomycin A3 (Josamycin) in severe and very severe community-acquired pneumonia in Filipino children 2-5 years old (a pilot study) started with Philippines team. Rapid diagnostic test for rapid diagnosis of infection with adenovirus and respiratory syncytial virus was evaluated with Vietnam team.</u>

#### Vietnam

Set up laboratory in Vietnam National Children's Hospital (VNCH) for research of basic field in Vietnam. The funding from project which support for some equipment in lab as a deep freezer and Luminex system. Transfer of protocol for risk factors of severe pneumonia induced by H5N1 and H1N1pdm 2009 to VHNC and Philippines from Teikyo University, Tokyo, Japan. Rapid diagnostic test for rapid diagnosis of infection with adenovirus and respiratory syncytial virus was evaluated with Japan team.

#### Philippines

The project was an exploratory descriptive study to determine if cytokines could be identified in NP swabs that were positive for influenza virus in children with community-acquired pneumonia (CAP). The primary objective of the study was to identify 27 cytokines/chemokines from NP swab and blood, collaborating with Japan team.

The study was conducted at RITM in Muntinlupa City and the Philippine General Hospital (PGH). From May 2016 to November 2016, out of 70 children enrolled, 69 were included in the analysis. With 31 out of 69 cases, or 45% of the total respiratory isolates from the pneumonia cases, the Respiratory Syncytial Virus (RSV) was 19 cases out of a total of 69 cases, or 28% of the total cases. Adenovirus was,11 out of 69 cases, or 16% of the total cases. There were 7 cases of MPV, or 10% of cases. Bocavirus, HEV, and OC43 had equal frequency of occurrence, with 4 cases each. Influenza identified by PCR remains at 2 out of 69, or 3% of the total cases.

#### <u>TB team</u>

Japan

We characterized the Indo-Oceanic lineage (lineage 1) of *Mycobacterium tuberculosis* (MTB) including EAI strains genotypically, because it is a unique genotype spreading in Vietnam and the Philippines. The findings will be useful to detect possible export and import of unique MTB strains across countries.

#### Vietnam

Patients living in Da Nang city, Vietnam, who suffered from smear positive pulmonary TB were recruited. After providing informed consent, the patients took interview and provided sputum samples for culture. MTB isolates collected from positive culture samples were used for DNA extraction and drug susceptibility testing. DNA samples were sent to Japan for molecular analyses. To implement the project, new techniques were transferred from Hanoi Lung Hospital and the Research Institute of Tuberculosis – JATA, Japan.

#### Philippines

MTB isolates were obtained from sputum samples of TB patients of a community-based TB surveillance study in a rural area in the Philippines. Out of 1,622 participants with presumptive tuberculosis, 468 (28.8%) were diagnosed to have tuberculosis. The annual tuberculosis case notification rate in San Juan was 212 per 100,000 population. Out of the 210 MTB isolates tested for antimicrobial resistance, 49 (23.3%) were resistant to any drug. Resistance to isoniazid was common at 33 (15.7%), multi-drug resistant tuberculosis was 1.9%.131 isolates remained viable and sent for molecular analysis. The molecular strains from the analysis will be compared with demographic data, antimicrobial resistance patterns of the MTB isolates, and treatment success rates of the patients.

#### 5. Outputs and Anticipated Outcomes of Joint Research

#### 5-1 Scientific achievements and implemented activities of the joint research

#### <u>Flu team</u> Japan

Participate of meeting to report of resulting project 4 times in Japan, Vietnam and Philippines for diagnosis, treatment and research of cytokines/chemokines in influenza patients. Contributions of Rapid diagnostic test for rapid diagnosis of infection with adenovirus and respiratory syncytial virus was evaluated with Vietnam team and clinical trial (pilot) has been organized in Philippines.

#### Vietnam

Diagnosis of influenza by realtime PCR and RT-LAMP and multiplex PCR for 194 specimens. Specimen of patients with influenza will be collected to analyze NS1 gene and other risky genes of influenza virus to compare three countries. We have *in vitro* experimental using protocol from Japan side. We detect influenza A with subtype H1N1pdm 2009 and influenza B. Protocol for sequencing of whole genome of influenza B was followed protocol of Japan group. Rapid diagnostic test for rapid diagnosis was evaluated with Japan team. Establishment of research work in Vietnam and Philippines using research protocols established in Japan.

#### Philippines

- 1. Provided evidence of the presence of virus in nasopharyngeal specimens (NPS) collected from the children diagnosed with CAP.
- 2. Although influenza was not a significant virus detected in the NPS, other viruses were found providing crucial evidence that virus-associated childhood CAP is very common.
- 3. Initial findings of analysis showed the presence of cytokines in some blood and NPS. Levels of the cytokines are still being analyzed.
- 4. Clinical trial (pilot) has been organized by Japan team

#### <u>TB team</u>

#### Japan

MTB strains isolated from catchment areas In DaNang, Vietnam, and Batangas, the Philippines were compared with those in Japan. In DaNang, EAI4+5 > Beijing genotype in frequency, whereas in Bagangas, a majority was EAI2, indicating that EAI strains are spreading extensively in these areas. In Japan, Beijing genotype strains account for 70-80%, and EAI strains are very rare. Considering differences in distribution of the strains, routine genotyping sets including VNTR and spoligotyping should be optimized in each country.

#### Vietnam

During the study period, 220 patients with smear positive pulmonary TB were recruited from Da Nang city, of which new patients accounted for 85.9% and re-treated cases accounted for 14.1%. The majority of patients were male (81.8%), as often reported in Vietnam. The median of age was 45.1 years old (inter-quartile range 33.1-53.5 years old). Among 182 patients (82.7%) who agreed to perform HIV testing, no positive cases were detected. About 22.7% (50/220) of the patients had hemoptysis, whereas 27.3% (60/220) had dyspnea at the time of diagnosis.

Most of the patients (85.0%) had infiltration and 34.6% had cavities on chest radiographs. In 32/220 patients (2.5%), the culture of sputum samples revealed negative or contaminated. All of the remaining samples with positive culture results (188) were going to drug susceptibility testing and 170 of them provided interpretable results.

Among the four first-line anti-TB drugs, isoniazid, rifampicin, ethambutol and streptomycin, the proportion of samples showing resistance to any drug was 29.4% and multi-drug resistance defined by resistant to both isoniazid and rifampicin accounted for 4.7%.

DNA samples of the MTB were extracted successfully from 187 samples and were sent to Japan for molecular genotyping analyses.

#### Philippines

In October 17-18, 2016, the "e-Asia Project Implementation Workshop on Pulmonary Infectious Diseases induced/associated with Influenza and TB in Asian Countries' was

conducted.

#### 5-2 Synergistic effects of the international joint research

#### <u>Flu team</u>

Specimen of patients with influenza will be collected to analyze NS1 gene and other risky genes of influenza virus to compare three countries. Establishment of research work in Vietnam and Philippines using research protocols established in Japan.

The results of the Philippine study provide information to other e-Asia countries of the importance of other viruses to be associated with very severe hospitalized CAP in children. Moreover, like influenza, cytokines were also detected in these non-influenza virus-associated pneumonia cases. It has been published under collaboration Japan and Vietnam that rapid diagnostic test for rapid diagnosis of infection with adenovirus and respiratory syncytial virus was evaluated.In addition, <u>Clinical trial to evaluate the effect</u> of Leucomycin A3 (Josamycin) in severe and very severe community-acquired pneumonia in Filipino children 2-5 years old (a pilot study) started collaborating with Japan and Philippines.

#### TB team

Japan team focused on unique MTB genotypes spreading in Vietnam and the Philippines. Through this joint research, the two countries recognized more about characteristics of their indigenous MTB strains, whereas Japan deepened the knowledge about currently increasing foreign-born TB, particularly coming from major Southeast Asian countries, the Philippines and Vietnam.

New techniques can be transferred to Vietnam, serving for clinical practice or research activities on TB. The situation of TB including drug resistant can be investigated in the study area located in the middle area of Vietnam. Clinical information in combination with the results obtained from molecular genotyping analyses conducted by Japanese side can provide useful information on the characteristics of MTB lineages/sublineages circulating in this area.

Philippines team was able to be updated and to be trained on the latest techniques for molecular characterization of MTB. This has also improved capability of performing molecular epidemiology studies on the circulating *M. tuberculosis* strains in the Philippines. There is a need to know more about the EAI2\_Manillae strain due to the lack of literature on the molecular characterization and behavior of this TB strain.

#### 5-3 Broader impacts including contribution to society

#### Flu team

Japan

Preparedness to pandemic influenza such as bird flu H5N1 like in Japan-Vietnam-Philippines and the world. Also, drug innovation for preparedness to severe pneumoniae induced with pandemic flu was performed.

#### Vietnam

Research protocols and techniques have been successfully exchanged between Japan and Vietnam, also Japan and Philippines. Establish protocol for screen diagnosis influenza and other respiratory virus from specimens and reply as soon as possible for doctors as well as the first time establish basic research in influenza field in hospital in Vietnam.

#### Philippines

The influenza-cytokine study conducted in the Philippines has contributed greatly to the knowledge of virus etiology of CAP in children. Provision of cytokine levels among these virus-associated pneumonia cases will hopefully lead to newer strategies of managing CAP, like the use of immune-modulators. Clinical trial of Josamycin has been proceeded for reduction of severe pneumoniae.

#### TB team

#### Japan

A part of EAI strains are widely spreading in Vietnam and the Philippines, and known as a cause of foreign-born TB in Japan. Because these EAI strains have a potential to spread among all Asians, understanding these strains is important in public health of all Asian countries.

#### Vietnam

The study results can contribute to the management of TB in Vietnam, as well as provide useful information on TB molecular epidemiology not only in the area but also in Japan and the Philippines, when the results are compared with those of that areas.

#### Philippines

Due to the improved capacity to do molecular characterization of M. tuberculosis, we will be able to understand and know more about the behavior and molecular characteristics of the predominant circulating strain of MTB in the Philippines which is the EAI2\_Manillae strain. This better understanding of this strain will help us develop better diagnostic tests and formulate more effective TB prevention and control programs in the Philippines.

#### 5-4 Development and sustainability of the cooperation

The study helped establish a good collaboration model among three countries, especially on clinical research, applying new and advanced techniques to bring about the best effect and results of the study.

#### <u>Flu team</u>

Among Japan, Vietnam and Philippines, we analyzed cytokine storm and etiology of fluinduced pneumoniae by the established protocol transferred from Japan team. Between Japan and Vietnam, viral infection associated with pneumoniae was analyzed. It has been published under collaboration Japan and Vietnam that rapid diagnostic test for rapid diagnosis of infection with adenovirus and respiratory syncytial virus was evaluated. Also, between Japan and Philippines, collaboration of cytokine storm in pneumonia and clinical trial for preparedness to severe pneumoniae in the next pandemic flu, collaborating with Philippines team.

#### TB team

We conducted technical transfer to counterparts about genotyping methods such as compact drug susceptibility tests, DNA extraction, the VNTR method, spoligotyping, and SNP genotyping. The participating countries will rearrange such techniques depending on their own situations and enhance the public welfare in this field.

Also, since TB is a priority research area in the Philippines, the Department of Science and Technology through the Philippine Council for Health Research and Development (PCHRD) has committed to support molecular epidemiologic researches on TB to better understand the predominant TB strain.

Based on this, further cooperation becomes more feasible.

## 6. Future Goals and Plan of Activities after the project period Flu team

#### Japan

Applying a new eASIA project "Etiology and epidemiology of Influenza-like illness (ILI);

Influenza virus, *M. tuberculosis*, *B. pertussis*for, *M. pneumoniae*, *B. pertussis* reparedness to new pandemic Bird Flu in Japan, Vietnam and Philippines"

The overall goal of the project is to identify the host and bacterial pathological factors that associated with severity of pertussis infection in infants in Vietnam.

Vietnam

The overall goal of the project is to identify the host and bacterial pathological factors that associated with severity of pertussis infection in infants in Vietnam.

#### Philippines

Cytokine is a risk factor for the development of severe CAP, then studies could be conducted to look into the role of immune-modulators like macrolides in attenuating or decreasing severity of CAP of any etiology. Clinical trial of Josamycin has been proceeded.

#### <u>TB team</u>

Japan

Molecular epidemiology of tuberculosis is a hot topic in the world. Recently in this field, whole genome sequencing technique was introduced.

#### Vietnam

Continue to look for international collaborative research projects.

#### Philippines

We plan to include the drug-resistant patients and their contacts enrolled in the program located in the same community. This proposal will also include molecular analysis of obtained isolates so that we can better understand the predominant TB strain in the Philippines.

#### 7. Recommendations and Comments to the Program

#### Japan

When a new clinical study is conducted, a long period of preparation and implementation is necessary. In this sense, three years in e-Asia project are too short to show the final results. Depending on the situation, extension of the project should be approved.

#### Vietnam

e-ASIA JRP program is necessary to continue support for 3 countries for a new project in infectious disease in the next stage.

#### Philippines

The e-Asia JRP program is a very important project that should continue to be offered to investigators in relevant countries. More specifically, studies on the control of pneumonia in children ought to be encouraged and funding provided.

## Annex: List of Scientific Achievements and Implemented Activities of the Joint Research

- 1 Original Publications (All Authors' Names, Title, Journal Name, Volume, Page, Year, DOI)
  - 1.1 Co-authored among research teams
  - (1) Phung TTB, Do HT, Iwamoto H, Suzuki K, Suzuki K. Rapid diagnostic test vs. realtime PCR for rapid diagnosis of infection with adenovirus and respiratory syncytial virus. ADC Letter for Infectious Disease Control 53-55
  - (2) Kawachi S, Phung TTB, Nguyen LT, Nunoi H, Suzuki S. Severe acute respiratory distress syndrome induced by influenza compared with other viral infections and effects of intravenous immunoglobulin infusion therapy in Vietnamese children. ADC Letter for Infectious Disease Control. 2016; 3: 30-35
  - 1.2 Published by single team
  - (1) Nguyen TT, Suzuki S, Sugamata R, Ito F, Tran DT, Yamamoto T, Kawachi S, Suzuki K. Hypothiocyanous Acid Suppresses PolyI:C-Induced Antiviral Responses by Modulating IRF3 Phosphorylation in Human Airway Epithelial Cells. Tohoku J. Exp. Med. 2018; 245: 131-140.
  - (2) Nguyen. TT, Suzuki S, Ito F, Sugamata R, Yamamoto T, Kawachi S, Suzuki S. Role of hypothiocyanous acid on the cytokine production in airway epithelial cells. ADC Letter for Infectious Disease Control 2017; 5:24-27
  - (3) Hishiki H, Kameoka Y, Kato Y, Itoh R, Someya T, Inoue N, Haraki M, Kurosaki T, Suzuki S, Ogawa T, Ishiwada N, Suzuki K. Molecular structure in gene mutation of neuraminidase of influenza virus type B isolated from swab of patients showing fever duration. ADC Letter for Infectious Disease Control. 2017; 4: 18-23
  - (4) Kato YS, Fukuia K, Suzuki K. Mechanism of a Mutation in Non-Structural Protein 1 Inducing High Pathogenicity of Avian Influenza Virus H5N1. Protein & Peptide Letters, April 2016; 23(4):372-378
  - (5) Yasuda H, Kawachi S, Suzuki K. Simulated pathogenesis of severe acute respiratory distress syndrome and leukopenia induced with influenza A/H5N1virus infection and its treatment with immunoglobulins. J Math Monographs 2016; 9: 89-104.
  - (6) Oshiro S, Tada T, Kameoka Y, Suzuki K, Ohmagari N, Miyoshi-Akiyama T, Kirikae T. Development and evaluation of immunochromatography to detect Gram-negative bacteria producing ArmA 16S rRNA methylase responsible for aminoglycoside resistance. J Microbiol Methods. 2015 Nov;118:159-63. doi: 10.1016/j.mimet.2015.09.005. Epub 2015 Sep 14.
  - (7) Okochi Y, Aratani Y, Adissu HA, Miyawaki N, Sasaki M, Suzuki K, Okamura Y. The voltage-gated proton channel Hv1/VSOP inhibits neutrophil granule release. J Leuko Biol. 2016; Jan;99(1):7-19. doi: 10.1189/jlb.3HI0814-393R. Epub 2015 May 19.
  - (8) Sugamata R, Sugawara A, Nagao T, Suzuki K, Hirose T, Yamamoto K, Oshima M, Kobayashi K, Sunazuka T, Akagawa KS, Omura S, Nakayama T, Suzuki. Leucomycin A3 (LM-A3), a 16-membered macrolide antibiotic, inhibits Influenza A virus infection and disease progression. J Antibiot (Tokyo). 2014 Mar;67(3):213-22. doi: 10.1038/ja.2013.132. Epub 2014 Feb 5.
  - (9) Shiga Y, Sugamata R, Iwamura C, Nagao T, Zao J, Kawakami K, Kawachi S, Nakayama T, Suzuki K. Effect of invariant natural killer T cells with IL-5 and activated IL-6 receptor in ventilator-associated lung injury in mice. Exp Lung Res. 2014 Feb;40(1):1-11. doi: 10.3109/01902148.2013.854518. Epub 2013 Nov 18.
- 2 Presentations at conferences (Speaker, Title, Conference Name, Location, Date, Type of Presentation, etc.)
  - 2.1 Co-authored among research teams
  - (1) Shoji Kawachi, Thuy Thi Bich Phung,Liem Thanh Nguyen, Hiroyuki Nunoi, Kazuo Suzuki. Severe acute respiratory distress syndrome induced by influenza compared with other viral infections and effects of intravenous immunoglobulin infusion therapy

in Vietnamese children. Tagaytay, Cavite in Philippines 18 Oct.2016

- 2.2 Published by single team
- Shoji Kawachi, Noriko Nakajima, Kazuo Suzuki. Analysis of ARDS 21 cases induced influenza in Hanoi-Vietnam. The 22<sup>nd</sup> MPO meeting Kyoto 2-3 Dec. 2016
- (2) Shoichi Suzuki, Masahiro Ogawa, Kenji Izuhara Role of OSCN- in Bronchialar epithelial cells : Part 1. The 22<sup>nd</sup> MPO meeting Kyoto 2-3 Dec. 2016
- (3) Tran Huu Dat, Ryuichi Sugamata, Akihiro Sugawara, Tomoyasu Hirose, Fuyu Ito, Kiyoko S. Akagawa, Toshiaki Sunazuka, Satoshi Omura, and Kazuo Suzuki. The inhibitory activity of macrolide derivatives in proliferation of 2009 pandemic influenza A/H1N1 viruses (H1N1pdm09). The 22<sup>nd</sup> MPO meeting Kyoto 2-3 Dec. 2016
- (4) Thuy Thu Nguyen, Shoichi Suzuki, Masahiro Ogawa, Kenji Izuhara Role of OSCNin Bronchialar epithelial cells : Part 2. The 22<sup>nd</sup> MPO meeting Kyoto 2-3 Dec. 2016
- (5) Kazuo Suzuki and Yusuke Kato. Structure analysis of NS1 consisted of avian influenza virus A/H5N1associated with severity fulmination of avian influenza, e-ASIA Project- International Symposium on Infectious Diseases, Tagaytay, Cavite in Philippines 18 Oct.2016
- (6) Kazuo Suzuki, Haruka Hishiki,Yosuke Kameoka,Yusuke Kato,Reiko Itoh,Tomohiro Someya,Nobue Inoue,Mana Haraki,Tomomichi Kurosaki,Shochi Suzuki,Tomoko Ogawa and Naruhiko Ishiwada. Molecular structure in gene mutation of neuraminidase of influenza virus type B isolated from swab of patients showing fever duration Tagaytay, Cavite in Philippines 18 Oct.2016
- (7) Shoichi Suzuki. Airway inflammation induced by HOSCN Tagaytay, Cavite in Philippines 18 Oct.2016
- (8) Ryuichi Sugamata, Akihiro Sugawara, Tomoyasu Hirose, Tran H. Dat, Kiyoko S. Akagawa, Satoshi Omura, Toshiaki Sunazuka and Kazuo Suzuki Development of novel anti-influenza A virus drug based on 16-membered macrolide derivatives, e-ASIA Project- International Symposium on Infectious Diseases, Tagaytay, Cavite in Philippines 18 Oct.2016
- (9) Ryuichi Sugamata, Akihiro Sugawara, Tomoyasu Hirose, Tran H. Dat, Kiyoko S. Akagawa, Satoshi Omura, Toshiaki Sunazuka and Kazuo Suzuki Development of novel anti-influenza A virus drug based on 16-membered macrolide derivatives. 23th Macrolide Research. Tokyo, 2016.7.29-30.
- (10) Shoichi Suzuki, Masahiro Ogawa. Role of OSCN- in Bronchialar epithelial cells : Part 2. the21st MPO meeting, Tokyo, 31st Oct 2015
- (11) Thuy Thu Nguyen, Shoichi Suzuki, Ai Ikejiri, Masamichi Ohima, Fuyu Ito, Ryoichi Sugamata, Thuy Phung, Shoji Kawachi, Kazuo Suzuki Roles of NS1 of H5N1 influenza viruses inducing ARDS the21st MPO meeting, Tokyo, 31st Oct 2015
- (12) Ryuichi Sugamata, Akihiro Sugawara, Tomoyasu Hirose, Tran Dat, Toshiaki Sunazuka, Kiyoko Akagawa, Satoshi Omura, and Kazuo Suzuki Macrolide-based drug development for influenza focused on neutrophilic MPO, the21st MPO meeting, Tokyo, 31st Oct 2015
- (13) Thuy Thu Nguyen, Shoichi Suzuki, Ai Ikejiri, Masamichi Ohima, Fuyu Ito, Ryoichi Sugamata, Thuy Phung, Shoji Kawachi, Kazuo Suzuki Roles of NS1 of H5N1 influenza viruses inducing ARDS the21st MPO meeting, Tokyo, 31st Oct 2015
- (14) Shoici Suzuki, Thuy Thu Nguyen, Reiko Ito, Kazuo Suzuki, Contribution of Influenza viral non-structure protein1 and myeloperoxidase to induction of cytokines/chemokines. The 20th MPO meeting Shizuoka 7-8 Nov. 2014
- 3 Organization of workshops, seminars, symposia, etc. (Organizer, Title of Event, Date, Location, Number of Participants, etc.)

Date	Title of Event (Location)
1) 2014.1.16-19	Kick-off meeting (Tokyo)
2) 2014.1.19	Symposium (Tokyo)

- 3) 2014.3.3-6 Annual Joint Meeting (MOST-NHP, Vietnam) 4) 2015.1.15-17 Annual Joint Meeting (Tokyo) Project Progress (Bangkok, Thailand) 5) 2015.10.12 Annual Joint Meeting (NHP, Vietnam) 6) 2015.11.9-10 Progress Meeting (NHP, Vietnam) 7) 2016.2.25-27 8) 2016.2.28-3.2 Progress Meeting (RITM, Philippines) Progress Meeting (NHP, Vietnam) 9) 2016.5.2-6 10) 2016.6.22-25 Progress Meeting (RITM, Philippines & NHP, Vietnam) Annual Joint Meeting (RITM & Tagaytay, Philippines) 11) 2016.10.17-19 Josamycin Protocol Preparation (UP-PGH, Philippines) 12) 2017.1.22-23 Progress Meeting (NHP, Vietnam) 13) 2017.2.19-22 Josamycin Transport (UP-PGH, Philippines) 14) 2017.3.12-14
- 4 Researcher exchanges including students (Description of Exchange, Destination, Duration, etc.)

Ms. Nguyen Minh Hang (VNCH, Vietnam) Dr. Nguyen Thi Ngoc Tran (VNCH, Vietnam) Dr. Doan Thi Mai Thanh (VNCH, Vietnam) Ms. Inez Andrea P. Medado (Philippines) Ms. Hannah Leah E. Morito (Philippines) Associate Prof. Neil Andrew Bascos (Philippines)

Two staff members of the Microbiology Department of Da Nang Lung hospital took training courses in the Research Institute of Tuberculosis JATA in Nov 2014 and Hanoi Lung Hospital in Feb 2015.

Japanese researchers from the Research Institute of Tuberculosis JATA came to Da Nang Lung hospital for technical transfer and monitoring of the project's implementation.

- 5 Number of patent applications None
- 6 Awards

#### Prof. Suzuki and Prof. Kawachi

2016 Medal for People's Health from the Ministry of Health, Vietnam





#### Prof. Suzuki

2016 Visiting Professor in Vietnam National Children's Hospital in Hanoi



7 Others (Including agenda of workshop, photos of research teams, meetings, and etc.) **Agenda of Symposium** 

2014

e-ASIA Project International Symposium 2014.1.18 Teikyo University, Japan

#### e-ASIA Project International Symposium

#### Pulmonary Infectious Diseases induced associated with Influenza and TB in Asia



- 22

# Saturday, January 18, 2014 09:30 - 18:00 ADC Teikyo University Itabashi Campus 2F Meeting Room

	Chair	Kazuo Suzuki	ADC Institute, Teikyo University	Director-General
Opening		Kazuo Suzuki	ADC Institute, Teikyo University	Project Leader
About e-ASIA Project	Cha	Kazuo Suzuki	ADC Institute, Teikyo University	Director-General
Introduction of e-ASIA Activities	JRP	1) Kiyoshi Kita	Japan Science and Technology Agency (JST) Department of Biomedical Chamittery Graduate Science of	Program Officer, e-ASIA JRP Professor
		2) Geng Tu	Medicine, The University of Tokyo Department of International Affairs, IST	Manager
Overview of e-AISA Project		Kazuo Suzuki	Teikyo University	Project Leader
Introduction of Project Lead	lers in Vie	tnam and Philip	pines	
Introduction of Project Men	nbers in Ja	apan, Vietnam a	nd Philippines by the leaders	
1) influkenza team		Japan, Vietnam Suzuki: Makimu	and Philippines ura, Sunszuka, Inoue, Akagawa, Thuy,	Dra Marilla Lucero
2) TB team		Japan, Vietnam	and Philippines	
		Kato: Kacho, M	aeda, Thuong, Duc, Hang, Montoya	
			Lunch	
Summorium on Bui	Imonary li	nfectious Diseas	es induced associated with Influenza	and TB in Asia Countries
symposium on Pul		enza and its trea	atment	
Part 1: Preparation to Pand Suzuki (Japan) Sunazuka (Japan) Makimura (Japan) Thuy, Dien (Vietnam) Dra Marilla Lucero, Jaime ( Commentators: Makimur	emic Influ 5. Montoy 19. Sunazu	a (Philiopines) ka, Inoue, Akaga	wa	
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Part 1: Preparation to Paul Suzuki (Japan) Sunazuka (Japan) Makimura (Japan) Thuy, Dien (Vietnam) Dra Marilla Lucero, Jaime ( Commentators: Makimur Part 2:Global strategy for tu Kato: TB in Japan and the Maeda: Advance in molect Duc (Director of Danang T TB in Vietnam: further u Montoya (the Philippines)	emic Influ C. Montoy Berculosi world (15 B and Lun Inderstan : TB in tho	a (Philippines) ka, Inoue, Akaga s control and col min talk + 5 min miology and coll g Disease Hospit ding expected fix Philippines (20 r	wa Break untermeasures against tuberculosis p discussion) aborative studies in Asia (20 min talk al, Vietnam): om e-ASIA collaborativeproject. (20 m min talk + 10 min discussion). Break	revailing in Asian countries - 10 min discussion) in talk + 10 min discussion)

Reception (Restaurant in the Hosopital)

2015

e-ASIA Joint Research Program Meeting 2015.1.15-17 Teikyo University, Tokyo

	e-ASI	A Joir	nt Re	search	Program (e-ASIA JRP	) Meeting 201	.4FY
201	015 Session		Influenza Team		TB Team		
January	Time			Place		Place	
Thu 15	10:00 - 12:00	0:00 - 2:00		Teikyo	BL-2 Seminar	JATA	Meeting Rm
	12:00- 13:00			- L	Lunch at Telkyo University Lunch at JATA I		
	14:00 - 17:30			Joint Research Meeting at RIT in Suidobashi			
	73	1			Opening and overview	w	Kazuo Suzuki
		2			<b>Research Progress in</b>	n Inftuenza Team	
			2-1		In Japan		Kazuo Suzuki
	14:00 - 15:30		2-2		In Vietnam		Thuy Phung
			2-3		In Philippines		Marilla Lucero
			2-4		Short presentation-1		Shoichi Suzuki
					Short presentation-2		
	15:30 - 16:00			Break			
	16:00 - 17:30		3	Research Progress in TB Team			w.
			3-1		In Japan		Naoto Keicho
			3-2		In Vietnam		??
			3-3		In Philippines		Jimie Montoya
			3-4		Short presentation-1		<b>4</b> 4
					Short presentation-2		??
				Closing Remarks			Seiya Kato
	18:00 -			Di	iscussion and Reception	(	??
5410	9:00- 12:00	Team m	eeting	Teikyo Univ	BL2 Semi 5	ATA	?
Fri 10	13::00- 17:00	Team m	esting	Teikyo Univ	BL2 Semi 5	JATA	?
Sat 17	9:30~ 17:30	Int	ernat	tional N	leeting for e-ASIA JRP	Teikyo University,	Main Building
	9:30 - 11:45			Morn	ing Session	Meeting Room 5	
	11:45- 13:00		L	unch at 1	Feikyo University	Meeting Room 5	
	13:00: - 1730	Afternoon session Auditorium					
	18:00			Rec	eption at Restaurant in Te	eikyo University	
2	0		-				
jê.	25 - 32		-		*応言を参考た.応たにを発言した。	2	-

#### e-ASIA Joint Research Program Meeting

#### 2015.11.9-10 NHP, Hanoi, Vietnam

#### e-ASIA Project - International Symposium on Infectious Diseases Pulmonary Infectious Diseases induced associated with Influenza and TB in Asian Countries

	Monday, I	November 9, 2015 - 9:	00 to 17:00
09:00	Internal meeting - Influenza team	Influenza team	Venue: National Hospital of Pediatrics
09:00	Internal meeting - TB team	TB team	Venue: Hanoi Lung Hospital/NCGM-BMH MCC
	Tuesday, N	lovember 10, 2015 - 9	:30 to 16:30
	Conference room, Na	ational Hospital of Ped	iatrics, Hanoi, Vietnam
09.00	Opening Remarks Welcom to Vietnam	Assoc. Prof. Le Thanh Hai or Assoc. Prof. Le Thi Minh Huong	Director, National Hospital of Pediatrics Vice Director, National Hospital of Pediatrics
		Dr. Phung Thi Bich Thuy	Project Leader MOST
	Introduction	All attendees	
09:40	Speech	Somebody	Ministry of Science and Training, Vietnam
09:50	Overview of e-ASIA Project	Prof. Kazuo Suzuki	Project leader, Teikyo University ADC Instiutte
	Pro	ogress Report in Influe	enza and TB team
	Progress in 2015, Japan influenza		
10:10	team?	Prof. Kazuo Suzuki	Teikyo University
10:25	Progress in 2015, Japan TB team	Dr. Naoto Keicho	The Research Institute of Tuberculosis JATA
10:40	team	Thuy	National Hospital of Pediatrics
10:55	Progress in 2015, Vietnam TB team Progress in 2015, Philippines	Dr. Le Van Duc	Da Nang Hospital of TB and Lung Diseases
11:10	influenza team	Dr Marilla Lucero Prof laime	Research Institute for Tropical Medicine (RITM)
11:25	Progress in 2015, Philippines TB team	Montoya	UP College of Medicine and RITM
11:40	Discussion	Prof. Kazuo Suzuki a	nd All attendees
12:00	R	eception (Restaurant	in the Hospital)
	Symposium on Pulmonary Infection	Is Diseases induced as	sociated with Influenza and TB in Asian Countries
	From Japan: 20 min talk + 10 min	Dr Shoichi	e and its treatment
13:30	discussion	Suzuki	Project leader, Teikyo University ADC Instiutte
14:00	From Philippines: 20 min talk + 10 min discussion	Dr. Marilla Lucero	Research Institute for Tropical Medicine (RITM)
14:20	From Vietnam: 15 min talk + 5 min	Dr. Phung Thi Bich	
14:30	discussion	Tea-brea	
14.50	Part 2: Global strategy for tuberculosis	control and counterr	neasures against tuberculosis prevailing in Asian
	countries		
15:10	From Japan: 20 min talk + 10 min discussion	Dr. Seiya Kato	The Research Institute of Tuberculosis JATA
15:40	From Philippines: 20 min talk + 10 min discussion	Prof Jaime Montoya Dr. Pham Huu Thuong (	University of the Philippines College of Medicine
16:10	From Vietnam: 15 min talk + 5 min discussion	Dr. Nguyen Thi Le Hang	Hanoi Lung Hospital/ NCGM-BMH MCC
16:30	Closing Remarks	Dr. Pham Huu Thuong	Hanoi Lung Hospital/ NCGM-BMH MCC

2016	
e-ASIA Joint	Research Program Meeting
2016.10.18	Taal Vista Hotel, Tagaytay, Cavite

8:30am	Registration	
9:00am	Welcome Remarks	Dr. Alexander Madrigal
		Regional Director, DOST IV-A
	Introduction	
9:10am	Message	Sec. Fortunato dela Peña
		Secretary, DOST
		USec. Rowena Cristina Guevara
		Undersecretary for R&D, DOST
9:20am	Overview of e-ASIA Project	Prof. Kazuo Suzuki
		Project Leader e-Asia Project for Influenza and
		ТВ
		Teikyo University ADC Institute, Tokyo, Japan
9:30am	Photo Op	
	Coffee Break	
	Presentation of Progress Report (Japan)	
10:00am	Influenza Team	Prof. Kazuo Suzuki
		Teikyo University, Tokyo, Japan
	Open Forum	
10:20am	Tuberculosis Team	Dr. Seiya Kato
		The Research Institute of Tuberculosis JATA,
		Tokyo, Japan
10:40am	Tuberculosis research agenda in the	Dr. Seiya Kato
	context of globalization	The Research Institute of Tuberculosis JATA,
40.50		lokyo, Japan
10:50am	Molecular characteristics of	Dr. Naoto Keicho, Maeda Shinji, Dr. Kato Seiya
	MIB strains in Da Nang	The Research Institute of Tuberculosis JATA,
	Open Forum	
	Presentation and Discussion of	
	Progress Report (Vietnam)	
11:05am	Influenza Team	Dr. Phung Thi Bich Thuy
		National Hospital of Pediatrics, Hanoi Vietnam
	Open Forum	
11:25am	Tuberculosis Team	Dr. Le Van Duc
	e-ASIA project: Tuberculosis,	Da Nang Hospital of TB and Lung Diseases, Da
	Vietnamese component: Progress	Nang, Vietnam
	report 2016	
	Open Forum	
	Presentation and Discussion of	
	Progress Report (Philippines)	
11:45	Influenza Team	Dr. Marilla Lucero
		Research Institute for Tropical Medicine (RITM)
	Open Forum	
12:05	Tuberculosis Team	Dr. Jaime C. Montoya
		University of the Philippines-College of Medicine
	Open Forum	

12:25pm	Lunch	
1:30pm	Overview of Influenza and severe	Prof. Kazuo Suzuki
	pneumonia	Teikyo University, Tokyo, Japan
1:40pm	Structure analysis of NS1 consisted of	Prof. Kazuo Suzuki and Yusuke Kato
	avian influenza virus	Asia International Institute of Infectious Disease
	A/H5N1associated with severity	Control, Teikyo Univeristy, Tokyo, Japan
	fulmination of avian influenza	
1:50pm	Molecular structure in gene mutation	Prof. Kazuo Suzuki , Haruka Hishiki, Yosuke
	of neuraminidase of influenza virus	Kameoka,Yusuke Kato,Reiko Itoh,Tomohiro
	type B isolated from swab of patients	Someya, Nobue Inoue, Mana Haraki, Tomomichi
	showing fever duration	Kurosaki,Shochi Suzuki,Tomoko Ogawa and
		Naruhiko Ishiwada
		Asia International Institute of Infectious Disease
		Control, Teikyo Univeristy, Tokyo, Japan
2:00pm	Airway inflammation induced by	Dr. Shoichi Suzuki
	HOSCN	Asia International Institute of Infectious Disease
		Control, Teikyo Univeristy, Tokyo, Japan
2:10pm	Severe acute respiratory distress	Prof. Shoji Kawachi, Thuy Thi Bich Phung, Liem
	syndrome induced by influenza	Thanh Nguyen, Hiroyuki Nunoi, Kazuo Suzuki
	compared with other viral infections	Asia International Institute of Infectious Disease
	and effects of intravenous	Control, Teikyo Univeristy, Tokyo, Japan
	immunoglobulin infusion therapy in	
	Vietnamese children	
2:20pm	Development of novel anti-influenza	Dr. Ryuichi Sugamata
	virus drug based on 16-membered	Asia International Institute of Infectious Disease
	macrolide derivatives	Control, Teikyo Univeristy, Tokyo, Japan
2:30pm	Developing diagnosis method for	Dr. Thuy Thi Bich Phung
	infectious diseases in Vietnam National	Vietnam National Children's Hospital, Hanoi,
	Children's Hospital	Vietnam
2:40pm	Clinical characteristics of pertussis's	Dr. Tran Minh Dien, Nguyen Trong Thanh, Le Thi
	patients in the Viet nam National	Thuy Dung, Trinh Xuan Long, Ta Anh Tuan,
	Hospital of Pediatrics, in 2015	Nguyen Van Lam
		Vietnam National Children's Hospital, Hanoi,
		Vietnam
2:50pm	Open Forum	
3:00pm	Presentation of the proposal on Clinical	Dr. Salvacion Gatchalian
	Trials (Pilot Study)	UP-Philippine General Hospital
	Open Forum	
3:20pm	Discussion of Future Plans for East	Facilitator: Prof. Kazuo Suzuki
	Asia Project	Asia International Institute of Infectious Disease
		Control, Teikyo Univeristy, Tokyo, Japan
4:30pm	Closing Remarks	



### 50th Anniversary of Teikyo University ADC International Symposium 帝京大学創立50周年記念ADC国際シンポジウム

Organizer:

Prof. Kazuo Suzuki, Director of Asia International Infectious Disease Control (ADC), Teikyo University



#### **Opening Remarks 13:00-13:05**

Session I Infectious Diseases (感染症) 13:05-15:10 Clinical characteristics of pertussis's patients in the Vietnam National Hospital of Pediatrics, in 2015 (ベトナム国立小児病院の百日咳) Associate Prof. Tran Minh Dien, Vice Director of the National Children's Hospital, and Hanoi Medical University, Hanoi, Vietnam Chair Dr. Nguyen Huu Tu, Kansai Medical University, Osaka, Japan Smallpox eradication (天然痘撲滅) Prof. Takeshi Kurata, International University of Health and Welfare & NIID, Former Director- General, Japan Chair Visiting Prof. Shoji Kawachi, ADC, Teikyo University, Tokyo, and Tomakomai City Hospital, Tomakomai, Japan
<b>Diversity of parasite mitochondria -as drug targets-</b> (寄生虫ミトコンドリアの多様性一薬剤
標的として一) Prof. Kiyoshi Kita, Nagasaki University, School of Tropical Medicine and Global Health, Nagasaki,
Japan Chair Prof. Tomoko Yamamoto, ADC, Teikyo University, Tokyo, Japan
<b>Tuberculosis research agenda in the context of globalization</b> (グローバル化における結核研 究)
Dr. Seiya Kato, Vice Director, Research Institute of Tuberculosis, Tokyo, Japan Chair Visiting Prof. Kiyoko Akagawa, Kitasato Institute, Tokyo, Japan.
Session II Host Defense and Vaccination(生体防御・ワクチン)15:45-17:45
Regulation of Influenza A Virus Pathogenicity by NADPH Oxidases (インフルエンザと活性酸素)
Dr. Stavros Selemidis, Department of Pharmacology, Monash University, Clayton, Australia. Chair Prof. Yasuo Ono, Teikyo University, Tokyo, Japan
<b>Human Immunity to Chikungunya Viruses: Prospects for Vaccine</b> (ワクチン) Prof. Pratima Ray, Department of Biotechnology, Faculty of Science, Jamia Hamdard University, New Deli, India Chair Prof. Koichi Makimura, Teikyo University, Tokyo, Japan
<b>Molecular epidemiology and pathogenesis of virus gastroenteritis</b> (ウイルス性胃腸炎の分子
没字と病態について) Prof. Hiroshi Ushijima, Department of Microbiology, Nippon University School of Medicine, Tokyo,
Japan Chair Prof. Masakazu Mimaki, Teikyo University, Tokyo, Japan <b>Closing Remarks 17:45-18:00</b>
Reception 18:00 - Dining Room of Hospital

#### Photos Joint Meeting: Japan-Vietnam-Philippines











Annual Joint Meeting Japan-Vietnam-Philippines NHP, Vietnam, Nov. 9-10, 2015



Annual Joint Meeting Japan-Vietnam-Philippines RITM & Tagaytay, Philippines Oct. 16-20, 2016



#### Individual Meeting



Progress Meeting in RITM, Philippines March 29, 2016



Progress Meeting in NHP, Vietnam May 5, 2016



#### Others



Training in Japan and on-site technical transfer in Da Nang Lung hospital



Japanese team visited Da Nang Lung hospital



#### Clinical Trial with LMA<sub>3</sub> (Josamycin)

<text><text><text><text><text><text><text><text><text><text><text></text></text></text></text></text></text></text></text></text></text></text>	Frs. Kazuo Suzuki, Sally Gatchalian, Shoji Kawachi
又は公益社団法人相本医師会が設置している公園データベース に、当該研究の概要をその実施に先立って登録すること。 2. 研究許両書の変更及び研究の進捗に応じて、当該データベースへ の登録内容を直定更新すること。 3. 研究を終了したときは、遅滞なく、当該研究の結果を当該データ	Josamycin (LMA3)
ペースに登録すること。 以上	at
	Department of Pediatrics Philippine General Hospital, University of the Philippines/Manila March 14, 2017