Internal Ex-Post Evaluation for Technical Cooperation Project **(SATREPS)**[1]

conducted by Thailand Office: July, 2019

Country Name	**The Project for Research and Development of Therapeutic Products against Infectious Diseases, Especially Dengue Virus Infection**
Kingdom of Thailand	

I. Project Outline

Background	In Southeast Asia with large population, there were many incidences of reemerging infectious disease, including dengue fever, influenza and botulism. It was concerned that global outbreaks of these diseases would have occurred from Southeast Asian countries. On the other hand, there is only symptomatic treatment of Dengue virus infection but no therapeutic product in practical use. For the avian influenza, an emerging infectious disease, it was necessary to develop medicine for effective remedy while antiviral drugs were used. For botulism, it was necessary for Thailand, where the historical outbreak had occurred in 2006, to develop new therapeutic products particularly. The level of Thai researchers in the area of infectious diseases was relatively high in the neighboring countries. However, they needed to undertake their capacity and skills improvement for development of new therapeutic products using cell technology and biotechnology. Also, it was essential to establish efficient and effective system for development of pharmaceutical products under cross organizational cooperation among stakeholders, including the National Institute of Health and universities.		
Objectives of the Project	Through establishing necessary system for experiments and studies for human monoclonal antibodies (HuMAb) against the target viruses including dengue virus, development of novel bioactive compounds against dengue virus and setting up laboratories and Standard Operating Procedures (SOPs), the project aimed at improvement of research and development capacity of therapeutic products against infectious diseases, including dengue hemorrhagic fever in Thai research institutes, thereby contributing to promotion of research and development of pharmaceutical products against dengue hemorrhagic fever and other infectious diseases. 1. Overall Goal: N.A. 2. Project Purpose: Research and development capacity of therapeutic products against infectious diseases, especially dengue hemorrhagic fever is improved in Thai research institutes through the collaborative research.		
Activities of the Project	1. Project site: Bangkok and Nonthaburi 2. Main activities: 1) Establishment of necessary systems for experiment of HuMAb, evaluation of effectiveness and safety of studies, for cloning of human MAb IgG variable regions and expression of the human recombinant MAb, 2) Identification, screening and evaluation of novel bioactive compounds against dengue virus, 3) Setting up laboratories and SOPs 3. Inputs (to carry out above activities) Japanese Side 1) Experts: 28 persons 2) Trainees received: 31 persons 3) Equipment: Safety cabinets, high performance liquid chromatography, fluorescence microscopes, etc. Thai Side 1) Staff allocated: 46 persons 2) Land and Facilities: Office and research spaces, including Bio-Safety Level (BSL)-2 laboratories in the National Institute of Health and Mahidol University 3) Local cost: cost for renovation of laboratory space and 24 hour electricity for lab and equipment in the Faculty of Tropical Medicine of MU and NIH		
Project Period	July 2009–July 2013	Project Cost	(ex-ante) 401 million yen, (actual) 367 million yen
Implementing Agency	National Institute of Health (NIH), Department of Medical Sciences (DMSc), Ministry of Public Health Faculty of Tropical Medicine and Faculty of Science, Mahidol University (FTM-MU)		
Cooperation Agency in Japan	Research Institute of Microbial Diseases, Osaka University (RIMD-OU) International Center for Biotechnology, Osaka University Medical & Biological Laboratories, Co., Ltd.		

II. Result of the Evaluation

< Special Perspectives Considered in the Ex-Post Evaluation >

[Overall Goal]

Although the Overall Goal had not been set in the project design, the followings were regarded as envisaged Overall Goals in the terminal evaluation report. Therefore, achievement levels of these envisaged Overall Goals were verified as "actions for utilization of research outcomes", one of "the expected positive impacts" by this ex-post evaluation.

- Final candidate(s) of HuMAb with anti-dengue activity are expected to be subjected to official pre-clinical trials by appropriate Good Laboratory Practice (GLP)-compliant facilities such as pharmaceutical enterprises.
- The research techniques provided by the project are expected to be utilized for other pharmaceutical development by Thai side after the end of the project period.

1 Relevance

<Consistency with the Development Policy of Thailand at the Time of Ex-Ante Evaluation and Project Completion>

The project was consistent with the Thailand's development policy such as the "10th National Health Development Plan" (2007-2011) to prioritizing establishment of medical treatment system against emerging and reemerging infection diseases. The policy priority has not been changed during the project period.

[1] SATREPS:Science and Technology Research Partnership for Sustainable Development

<Consistency with the Development Needs of Thailand at the Time of Ex-Ante Evaluation and Project Completion >

The project was consistent with the Thailand's development needs for pharmaceutical products against dengue hemorrhagic fever, avian influenza and botulism.

<Consistency with Japan's ODA Policy at the Time of Ex-Ante Evaluation>

The project consistent was with the Japan's ODA policy for Thailand prioritizing support for human security including infectious diseases control through technical cooperation in the "Economic Cooperation Plan for Thailand" (2006).

<Evaluation Result>

In light of the above, the relevance of the project is high.

2 Effectiveness/Impact

<Status of Achievement of the Project Purpose at the time of Project Completion>

The Project Purpose was achieved by the time of project completion. DMSc obtained 21 candidate Human MAb with broad and strong neutralizing antibodies against dengue type 1-4 viruses by in-vitro testing. Three candidate clones were produced at Thai-NIH for in-vivo testing at Osaka University in Japan. FTM has produced 2 candidates neutralizing human monoclonal antibodies (NhuMAb) clone number 19 and 54 that successfully passed the dengue virus neutralization test; i) 20 clinical isolates virus, ii) Mice prior injected with dengue virus, iii) Marmoset monkey prior injected with 10 million dengue virus.

<Continuation Status of Project Effects at the time of Ex-post Evaluation>

The project effects have been continued by the time of ex-post evaluation. The main research outputs produced by the project, such as candidates for clinical trial for dengue have been utilized for further research and study since the project completion. DMSc has utilized three candidates for using in neutralizing antibody activities study. Also, FTM has utilized and improved two candidate dengue NhuMAbs clones for study on antibody germline for all 20 clones of NhuMAbs and Fc (fragment crystallizable)[2] modified to make NhuMAb with no virus enhancement

In addition, the Medical Biotechnology Center (MBC) and DMSc established the project "Research and development of recombinant of HuMAbs as a model. Immunoglobulin gene sequence from 3 candidate clones were synthesized and cloning to produce recombinant HuMAb. The native clones were produced and used for characterization and neutralizing activity comparison. Furthermore, the Center of Excellent for Antibody Research (CEAR) and FTM have launched 6 new research or study project for producing therapeutic products against dengue virus.

As mentioned above, both of NIH and FTM have been continuing to utilize the clones, the outputs of the project, for further research and studies. Also, NIH and FTM have been continuously used and maintained equipment installed by the project for their research works. In particular, the equipment installed at CEAR have been utilized by not only FTM but also by other departments in Mahidol University.

<Status of Achievement for Overall Goal at the time of Ex-post Evaluation>

The Envisaged Overall Goal 1 was partially achieved at the time of ex-post evaluation. By NIH, the final candidates of HuMAbs with Anti-dengue not yet been subjected to official pre-clinical trials by any appropriate GLP compliant facilities but they are looking for partner/granter to invest for the pre-clinical trial. By FTM, a pharmaceutical company from India signed contract with the Dean of FTM and the Assistant Professor/the Deputy Dean for Research and Innovation of FTM-MU/ the Director of CEAR, for industrial scale production of NhuMAb clone 19 & 54 and Fc modified clone 19 & 54 in Good manufacturing Practice (GMP) plant and further tested *in vitro* and *in vivo*.

The Envisaged Overall Goal 2 was achieved. MBC and DMSc of NIH have been utilizing the immunoglobulin gene cloning and characterization, transient gene expression of human Mab for development of recombinant antibody for therapeutic. FTM and researchers have been continuing to use laboratory techniques and equipment provided by the project for further researches, including research on industrial scale production of therapeutic products against dengue as mentioned above.

In addition, NIH has submitted four international patent applications on the human MAbs against dengue virus and botulinum under the Patent Cooperation Treaty. Also, FTM obtained one patent of dengue virus serotype neutralizing antibodies in USA and Antigenic peptide derived from dengue virus in 11 countries including Japan, Thailand and USA. Also, FTM produced 25 publications related dengue virus based on the researches by the project.

<Other Impacts at the time of Ex-post Evaluation>

There are some positive impacts of the project confirmed at the time of ex-post evaluation. No negative impact on environment was observed at the time of ex-post evaluation. The counterpart staff of the project and the researchers trained by the project have improved their skills so that they have been able to expand their research works such as development of several recombinant monoclonal antibodies. Also, research capacity of the FTM researchers who had been engaged in the project have improved and they have continued various research activities. In fact, two researchers got promoted to be an assistant professor, four researchers got Ph.D using research outputs by the project and got promotion to lecturer, one researcher and two research assistants are going to complete Ph.D using research outputs by the project, and one research assistant is going to start the Ph.D course abroad. In addition, some other research assistants have been studying at the MSc course and are going to obtain MSc. As a result of the enhanced research capacity and establishment of CEAR, FTM increased their competitive advantage on research techniques and facility as well as international collaboration research and publication.

<Evaluation Result>

Therefore, the effectiveness/impact of the project is high.

[2] Fc region is the tail region of an antibody that interacts with cell surface receptors.

Achievement of Project Purpose and Overall Goal

Aim	Indicators	Results
(Project Purpose) Research and development capacity of therapeutic products against infectious diseases, especially dengue hemorrhagic fever is improved in Thai research institutes through the collaborative research.	Candidates for clinical trials against dengue hemorrphagic fever are produced.	Status of the Achievement: Achieved (Continued) (Project Completion) ● Three candidate clones HuMAb were produced at Thai-NIH for in-vivo testing at Osaka University in Japan. ● FTM produced 2 candidates NhuMAb clone number 19 and 54 (Ex-post Evaluation) ● The research outputs have been utilized: ➢ Three candidate clones of 76F3, 84C and 80E5 for using in neutralizing antibody activities study by DMSc ➢ Candidates DENV NhuMAb of 19 and 54 from FTM using for study on antibody germline for all 20 clones of NhuMAbs, modifying to make NhuMAb with no virus enhancement.
(Envisaged Overall Goal) 1) Final candidate(s) of human Mab with anti-dengue activity are subjected to official pre-clinical trials by appropriate GLP-compliant facilities such as pharmaceutical enterprises.	N.A.	(Ex-post Evaluation) Partially achieved ● NIH: The final candidates of HuMAbs with Anti-dengue not yet been subjected to official pre-clinical trials by any appropriate GLP compliant facilities. ● FTM: The pharmaceutical company from India signed contract for industrial scale production of NhuMAb clone 19 & 54 and Fc modified clone 19 & 54 in Good manufacturing Practice (GMP) plant and further tested in vitro and in vivo.
2) The research techniques provided by the project are expected to be utilized for other pharmaceutical development by Thai side after the end of the project period.	N.A.	(Ex-post Evaluation) Achieved ● NIH: The Immunoglobulin gene cloning and characterization, transient gene expression of HuMAb have been utilized by MBC, DMSc for development of recombinant antibody for therapeutic. ● FTM and researchers continue using laboratory techniques and equipment provided by project for further research including industrial scale production of NhuMAb clone against dengue virus

Source：Terminal Evaluation Report, Completion Report for JST, Information provided by NIH and MU-FTM

3 Efficiency

The project cost was within the plan and the project period was as planned (the ratios against plan: 90% and 100%, respectively). The project outputs were produced as planned. Therefore, the efficiency of the project is high.

4 Sustainability

<Policy Aspect>

The National Vaccine Institute of Thailand has a policy to promote research and development for pharmaceutical products including dengue hemorrhagic fever, influenza and botulism. The National Economic and Social Development Plan is aiming to support the innovation obtained from basic research continuing to product development, in case of dengue.

<Institutional Aspect>

NIH has sustained the organizational arrangement for the research activities related to development of NhuMAb against dengue. The business unit under the DMSc will be established to utilize all research products, anyhow it depends on the budget allocation. DMSc has deployed 6 staff for licensing related to dengue. For continuing the research activities related to the project, NIH has been looking for partner or granter to provide financial support. As mentioned above, NIH continues to use all equipment provided by the project, such as inverted fluorescence microscopy, high speed centrifuge, and isocage unit and biosafety changing station, for routine works and research studies.

For FTM, CEAR has been established since 2009 until present, and has still maintained its research function to further develop NhuMAb against dengue and other related tropical diseases. CEAR/FTM has 10 researchers engaged in the research activities related to development of NhuMAb. The number of researches of CEAR/FTM has been sufficient for continuing the related research activities. Also, FTM has several arrangements with other institutions/organizations (4 Thai institutions, 3 private companies, and 5 international collaborations) for utilization of research outcomes of the project in order to promote further research and producing therapeutic products. The equipment installed by the project have been continuously utilized by FTM and other departments of the Mahidol University as mentioned above.

<Technical Aspect>

Since the research activities related to NhuMAb against dengue have been continued by NIH and FTM, the both of NIH and FTM has sustained and improved their research capacities as mentioned above. In particular, the researchers and the research assistant of FTM improved their capacity and skills through their Ph.D and MSc studies using the research outputs by the project.

<Financial Aspect>

NIH and FTM have continuously ensured necessary budget or fund to sustain and/or expand their research activities related to NhuMAb against dengue based on the research outputs and/or outcomes by the project. NIH has a budget of more than 1.9 million bahts in the fiscal year of 2017/18 allocated by DMSc for the research and development of recombinant of HuMAbs to apply in therapeutics, and 0.12 million bahts in the fiscal year of 2018/2019 for the Hybridoma collection project from DMSc as well. For FTM, although no budget data is available, they have secured necessary funds from not only the Thai institutions/organizations but also private companies as well as international collaboration as mentioned above.

<Evaluation Result>

Therefore, the sustainability of the effects through the project is high.

5 Summary of the Evaluation
The project partially achieved the Project Purpose and achieved one of the envisaged Overall Goals through the research activities on NhuMAb against dengue. The research activities using the research outputs and outcomes by the project have been continued and expanded through further enhancement of the research capacity of NIH and FTM. Considering all of the above points, this project is evaluated to be highly satisfactory.

III. Recommendations & Lessons Learned

Recommendations for Implementing Agency:

[For FTM and NIH]

- In order to make maximum use of the research outputs by this SATREPS project, FTM and NIH needs to continue their research activities based on the research outputs and to utilize them in various ways including education at the university for fostering younger researchers through collaboration with CEAR/Osaka University.

Lessons Learned for JICA:

- Involvement many institutions and agencies in one project gave good opportunities for sharing practicing and comparative advantage among stakeholders. In particular, through the activities under the SATREPS project, the related institutions including not only academic institutions but also government authorities were able to share the process of researches and make necessary collaboration for utilization of the research outputs. On the other hand, since the coordination among different stakeholders with various interests and mandates or responsibilities can be complicated, the functional coordination mechanism should be required for not only for the project implementation stage but also the post-project stage. In particular for the post-project stage, follow-up activities by JICA, such as dispatch of short-term experts to facilitate coordination among the stakeholders and organizing seminars for dissemination of the research outputs, can be helpful to promote appropriate planning for utilization of research outputs/outcomes after the post project period.

The Director of CEAR and researchers, FTM/Mahidol University with the awards from National Research Council, Thailand

FTM/Mahidol University on the process of Industrial scale production of NhuMAbs by stable expressed CHO cell