

## Evaluation Summary

1. Outline of the Project	
Country: The Kingdom of Thailand	Project Title: The Project for Research and Development of Therapeutic Products against Infectious Diseases, especially Dengue Virus Infection
Issue/Sector: Healthcare and medical treatment	Cooperation Scheme: Technical Cooperation Project (under the scheme of “ <i>Science and Technology Research Partnership for Sustainable Development: SATREPS</i> ”)
Division in charge: Health Division 2, Health Group 3, Human Development Department	Total Cost: 410 million JPY (As of a Preparatory survey)
Period of Cooperation	(R/D): 24/July/2010-14/July/2013
	Partner Country’s Implementing Organization: National Institute of Health, Department of Medical Sciences, Ministry of Public Health Faculty of Tropical Medicine and Faculty of Science, Mohidol University
	Supporting Organization in Japan: Research Institute for Microbial Diseases, Osaka University International Center for Biotechnology, Osaka University Medical & Biological Laboratories, Co., Ltd.
	Other Related Projects: not applicable
1-1 Background of the Project	
<p>Re-emerging infectious diseases, including dengue fever and other important infectious diseases such as influenza, are more common in Southeast Asia, and there is an international growing concern over pandemic of these infectious diseases from the region. In addition, a large-scale outbreak of botulism was observed in the Kingdom of Thailand (hereinafter referred to as “<i>Thailand</i>”) in 2006; and thus, as is obvious that the importance of these infectious diseases is high in the Kingdom of Thailand, it is of great significance to develop novel therapeutic products in Thailand assuming leading role in the Southeast Asia.</p> <p>Under these circumstances, the Government of Thailand requested the Government of Japan to implement the technical cooperation for enhancement of research competency of Thai research institutes through the development of therapeutic products against those infectious diseases. On the basis of the request from the Government of Thailand, JICA, under the framework of “<i>Science and Technology Research Partnership for Sustainable Development</i>” (hereinafter referred to as “<i>SATREPS</i>”) launched the four-year technical cooperation project entitled “<i>Research and Development of Therapeutic Products against Infectious Diseases, especially Dengue Virus Infection</i>” (hereinafter referred to as “<i>the Project</i>”) on July 15, 2009 under the implementation structure consisting of the National Institute of Health (hereinafter referred to as “<i>NIH</i>”), Department of Medical Science (hereinafter referred to as “<i>DMSc</i>”), the Ministry of Public Health (hereinafter referred to as “<i>MoPH</i>”)</p>	

and Faculty of Tropical Medicine (hereinafter referred to as “FTM”) and Faculty of Science (hereinafter referred to as “FS”), Mahidol University (hereinafter referred to as “MU”) as counterpart research institutes from Thai side, and Research Institute for Microbial Diseases (hereinafter referred to as “RIMD”) and International Center for Biotechnology (hereinafter referred to as “ICB”), Osaka University (hereinafter referred to as “OU”) and Medical & Biological Laboratories, Co., Ltd. (hereinafter referred to as “MBL”) as research institutes from Japanese side, and one (1) long-term JICA Experts (Project Coordinator) and a number of short-term Japanese researchers are dispatched as of the time of the Terminal Review.

## 1-2 Project Overview

### (1) 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.

### (2) Outputs

- 1) Human monoclonal antibodies (MAb) against dengue hemorrhagic fever, influenza and botulism are prepared and evaluated their effectiveness and safety in collaboration between Thai and Japanese researchers.
- 2) Novel bioactive compounds against dengue virus are explored from Thai natural microorganisms, including plant-, soil- and insect-derived bacteria, and evaluated their effectiveness and safety in collaboration between Thai and Japanese researchers.
- 3) The system on research of bio-products is streamlined.

### (3) Input(as of the Terminal Evaluation)

#### Japanese Side

Dispatch of JICA Experts: Long-term Expert: a Project Coordinator and a total of 163 researchers (Total Duration: 36.4M/M)

Provided Equipment: Safety Cabinets, High Performance Liquid Chromatography, Fluorescence Microscopes, etc. (Total Cost:JPY190,435,710)

Overseas Activities Costs:JPY 38,100,010

Costs for Carrying Equipment with JICA Experts: JPY 35,704,617

Training in Japan: 31 researchers (A total of 590 days/person)

#### Thai Side

Counterparts: 46 personnel (1 from DMSc, 29 from NIH and 16 from MU)

Land and Facilities: Office and research spaces in NIH and MU, Renovation of the laboratory space in Faculty of Tropical Medicine

Local Cost<sup>2</sup>:THB 9,470,640 (THB 8,962,350 from DMSc/NIH and THB 508,290 from MU)

<sup>2</sup> Breakdown of the Local Cost from MU is mainly utility costs for water, heating and lighting, communication, etc. Though MU haven't allocate specific budget for the Project, scientists involved in the Project have been partially utilizing their own external research funds obtained from the Thailand Research Fund for procuring reagents, maintenance of research instrument, etc.

2. Terminal Evaluation Team			
Members	Dr. Yusuke FUKUDA	Leader	Executive Technical Advisor to the Director General, Human Development Department, JICA
	Mr. Masanori ABE	Cooperation Planning	Program Officer, Health Division 3, Health Group 2, Human Development Department, JICA
	Dr. Yoichi INOUE	Evaluation and Analysis	Senior Consultant, Consulting Division, Japan Development Service Co., Ltd.
	Dr. Takeshi KURATA	Infectious Disease Control	Program Officer of the Japan Science and Technology Agency (JST) - SATREPS Professor, International University of Health and Welfare, Shioya Hospital (Observer)
	Dr. Masahiro HATSU	Planning and Evaluation	Senior Staff, Research Partnership for Sustainable Development Division, JST
Period of Evaluation	February 10, 2013 – February 23, 2013		Study Type: Terminal Evaluation
3. Summary of Evaluation Results			
3-1 Achievements			
(1) Output 1			
<p>With regard to dengue research that is prioritized in the Project several potential human MAb with strong and broad neutralizing activities were already prepared, and advanced animal tests using marmoset were got started beyond the framework of the Project. And also, several potential MAb for each of influenza virus and botulinum toxins have been prepared. Patent applications have been made and research papers have been published in each research subject even before the end of the project period. In addition, a number of Thai researchers have acquired various novel technologies in each research subject through the collaborative research activities as well as the Training in Japan; therefore, Output 1 is already achieved as of the time of the Terminal Evaluation.</p>			
(2) Output 2			
<p>Unfortunately, it is unlikely that final candidate compound(s), of which efficacy and safety were confirmed by in vivo testing, are determined by the end of the project period. However, as of the time of Terminal Evaluation, ICB-OU isolated from actinomyces and purified one (1) novel-structured compound with high anti-dengue activity and less cytotoxicity in in vitro, and determined its plain structure. In the months ahead, the Project decided to put priority for stereo-structure analysis over the in vivo efficacy and safety analysis using animals due to insufficient amount of purified compound. On the other hand, one (1) compound was purified at FS-MU and currently was subjected to plain structure analysis with support from the Toyama Prefectural University. Analytical work for plain structure determination is expected to be finished by the end of the project period.</p>			

### (3) Output 3

Experimental manipulations have been done in line with the Standard Operating Procedures (SOP) for standardized experimental protocols; also, the progress of research activities and consequent outcome have been monitored and for which information was shared amongst Thai and Japanese researchers through the Working Group Meetings and progress reports submitted by both Thai and Japanese researchers regularly. Thus, it is considered that the system on research of bio-products is generally established as of the time of the Terminal Evaluation.

### (4) Project Purpose

As aforementioned, sufficient research outcomes have been gained in each research subject as of the time of the time of the Terminal Evaluation. As for the main research subject of the development of human MAb for dengue virus, it is worth noting that the outcome is beyond our expectation and the Project has already started additional advanced researched as well as PR activities for pharmaceutical enterprises in order to shorten the distance to its pre-clinical trials.

In addition to this, Thai researchers have acquired a lot of knowledge and techniques and necessary research instrument has been equipped through the implementation of the Project; it can be considered that Project Purpose is generally achieved at the time of the Terminal Evaluation from a viewpoint of human resource and organizational development.

## 3-2 Summary of Evaluation Results

### (1) Relevance

The relevance of the Project is highly maintained as of the time of the Terminal Evaluation

With regard to the consistencies of the consistency of the Project Purpose with the Thai Health Policies, the needs of the target groups and Japan's Aid Policies that were confirmed at the Ex-ante Evaluation of the Project in December 2008, there wasn't any alteration of the Thai health policies as well as the needs so as to undermine the relevance of the Project.

Rationale for the development of 'therapeutic antibodies' for dengue virus, influenza virus and botulinum toxins are maintained as of the time of the Terminal Evaluation. Especially for dengue fever and dengue hemorrhagic fever, there have been no commercialized pharmaceuticals for the prevention as well as treatment of dengue viral infection; symptomatic treatment is only the way to cure. In recent years, the numbers of cases of dengue viral infections demonstrate an upward trend in urban areas in Thailand.

### (2) Effectiveness

The effectiveness of the Project is considered to be high at the time of the Terminal Evaluation.

The Project has already obtained human MAb with broad and strong neutralizing activities for each target pathogen of dengue virus and influenza virus in in vitro testing by the time of the Mid-term Review. After the Mid-term Review, the Project proceeded in vivo evaluation using marmosets mice (partially completed) for MAb against dengue virus and influenza virus, respectively; and it is highly anticipated that final candidates for these viruses be determined by the end of the project period. And

also, two (2) MAb with ant-botulinum type B toxin activity was obtained. Meanwhile, it is unlikely to determine final candidate of novel compound, of which efficacy and safety be confirmed in in vivo testing, by the end of the project period; but, several potential compounds with anti-dengue activity as well as lead compounds for future chemical modification have been obtained.

In addition, a lot of novel research technologies have been transferred to Thai research institutes through collaborative research activities, and necessary research instrument have been installed and utilized. For these reasons, certain improvements not only in research outcomes but also human resource/organizational development have been manifested through the implementation of the Project.

### (3) Efficiency

Though several unexpected external factors negatively affected smooth implementation of research activities at the initial phase of the Project, the efficiency of the Project is considered to be high from a broader point of view as of the time of the Terminal Evaluation.

At the initial phase of the, several unexpected external factors with regard to procurement procedures, practical operation of botulinum research and ethical approval for human MAb for dengue virus negatively affected the smooth commencement and full operation of the Project activities; however, the project activities have been accelerated owing to great efforts from both Thai researchers and Japanese Experts. Eventually, the delays didn't fatally affect the achievement of the Outputs of the Project at the time of the Terminal Evaluation.

Though many research institutes and subordinating laboratories were involved in the collaborative research of the Project, Japanese and Thai coordinators have put efforts in liaison and coordination amongst researchers, resulted in efficient operational management of the Project.

### (4) Impact

The following positive and/or negative impacts are confirmed and/or expected by the implementation of the Project.

The Japanese Chief Advisor of the Project, after the time of the Mid-term Review, has been enhancing his efforts to gain external research funds to raise data quality and quantity of the MAb for dengue virus. As the result, JST provided financial assistance for in vivo efficacy and safety evaluation using rhesus macaque and marmoset, which were beyond the scope of the Project. The evaluation work using marmoset is being conducted and expected completed by the end of the project period. In case that the evaluation were finished, the Project will be able to prepare a set of data to make presentations toward pharmaceutical enterprises. However, as common issues not only for dengue but also influenza and botulinum researches, the Project should set experimental conditions by taking practical clinical application of human MAb and/or novel compound(s) into consideration for better quality of data. Meanwhile, Thai counterpart institute have acquired various research techniques through the preparation of human MAb. As the acquired research techniques are applicable for other diseases such as malignant tumor and autoimmune diseases theoretically, it is anticipated that the target diseases can be extended in future. Nevertheless, it is necessary for Thai research institutes to receive technical and financial support by any means.

As a visible and positive impact of the Project A rapid diagnostic testing kit for novel influenza using a human MAb prepared by the Project on the basis of the immunochromatographic technology was developed in collaboration with a Japanese pharmaceutical and diagnostics manufacture. Consequently, the kit was commercialized by the manufacturer as an in vitro diagnostic device. As a collaborative research between Mahidol-Osaka Center for Infectious Diseases (MOCID) and a Japanese enterprise, a rapid diagnostic testing kit for dengue viral infection was developed using a MAb with neutralizing activity on the basis of the immunochromatographic technology, and being tested for its sensitivity and specificity as of the time of the Terminal Evaluation.

#### (5) Sustainability

A self-sustainability as well as a self-deployment of the benefits provided by the Project can be expected to some extent as of the time of the Terminal Evaluation.

From the political aspects, importance of countermeasures for dengue fever, influenza viral infection and botulism in Thailand are maintained, and it is assumed to be continued even after the end of the Project.

Not only the development of MAb for dengue virus other research subjects of the Project such as influenza research, botulinum research, and research for novel bioactive compounds, both Thai and Japanese research institutes have started their efforts to acquire external funding resources so that they can continue those researches even after the project period; but, it is desired that the efforts will be reinforced after the Terminal Evaluation from the financial viewpoint.

On the other hand, a lot of new technologies regarding preparation of human MAb and screening of novel bioactive compounds have been transferred through the implementation of the Project. Moreover, sufficient amount of equipment for research activities had been set up through the Project. Thus, technical sustainability can be anticipated to some extent.

### 3-3 Factors that promoted the attainment of the Project

#### (1) Concerning the project design

FTM-MU offered the research space dedicated to the Project and its renovation. That contributed to efficient implementation of experiments.

#### (2) Concerning the implementation process of the Project

- 1) Involvement of young researchers as well as graduate students with high motivation for acquisition of knowledge and skills for inexperienced technologies has substantially contributed to the acceleration of project research activities.
- 2) As for the dispatch of Japanese researchers, an elaborated dispatch plan for the Chief Advisor and Short-term Experts contributed to efficient project management. And also, the Project Coordinator (JICA Expert), with broad experiences for operational coordination, continued daily-basis communication with Thai coordinators and researchers. Under the pre-condition that many players are supposed to efficiently work together, not only Japanese and Thai coordinators have substantially contributed to smooth liaison and coordination and therefore efficient

management of the Project has been realized.

### 3-4 Factors that impeded the attainment of the Project

#### (1) Concerning the project design

Following two hindering factors were pointed out as of the time of the Mid-term Review. Afterwards, no major hindering factor was observed at the time of the Terminal Evaluation.

- 1) “*The approval is obtained by the ethical committee for the researches including the preparation of human MAb from patients' samples*” was stipulated in the PDM as a pre-condition of the Project, which should be fulfilled before the official commencement of the Project. However, it took approximately one and a half years for the Project to obtain the authorization of the research subject for preparation of human MAb against dengue virus at NIH, resulting in substantial delay in practical commencement of research activities for that.
- 2) With regard to the preparation of human MAb against botulinum toxin, it was revealed that there was little possibility for obtaining authorizations from the Thai Food and Drug Administration as well as the Ethical Committee at DMSc after the practical commencement of the Project. Accordingly, both Japanese and Thai sides agreed by exchanging a minutes of meeting that Japanese researchers with botulinum immunity were regarded as healthy volunteers (sample donor), from which samples obtained were used for the preparation of human MAb at Japanese research institutes. Afterwards, The human MAb will be brought to Thailand and subject to experiments of screening for specificity and titration of neutralization using botulinum toxin isolated at Thailand.

#### (2) Concerning the implementation process of the Project

At the initial phase of the Project, it took a longer time of one (1) year than anticipated for the procurement of research instruments, consumables, etc. necessary for the commencement of research activities at Thai research institutes in spite of the fact that the Project Coordinator had started preparation for the procurement, and it caused a substantial delay in the smooth initiation of research activities. The delay can be attributed to the time-consuming paperwork of tender procedures and custom clearance as one of major causes.

### 3-5 Conclusions

Though there are differences in the progress of research activities in individual research subjects as well as research groups, it is considered that the overall progress and achievements can be recognized as appropriate at the time of the Mid-term Review. And the concrete research outcomes enough to file international patent applications are already obtained; and thus, it is anticipated that the achievement of the Project Purpose of the Project can be attained to some extent by the end of the project period. However, the Project should set a detailed goal for each research subject with due consideration of future implementation of pre-clinical trials for efficient implementation of project research activities. As of the time of the Mid-term Review, review results of the Project on the basis of the performance of the project activities and its achievements as well as related information of the Project are as follows:

the relevance of the Project is maintained, and the effectiveness is generally high from the perspective of generation of research outcomes. Though the efficiency is at an intermediate degree since several unexpected external factors affected negatively, positive impacts derived from the Project can be anticipated in the future. Though there are several perspectives for the sustainability, overall sustainability can be anticipated to some extent as of the time of the Mid-term Review

### 3-6 Recommendations

1. The Project should complete the efficacy and safety testing using marmoset for remaining two out of three candidates of human MAb with neutralizing activity against dengue virus in Japan by the end of the Project period.
2. The Project should add final touches to establish the dengue experimental system for the evaluation using adult mice (Interferon-alpha/-beta/-gamma receptor-knockout mouse) by the end of the project period in order not only to reduce the experimental cost but also to acquire the quality data.
3. Not only in dengue but also influenza and botulinum researches, the Project should set experimental conditions by taking practical clinical application of human MAb and/or novel compound(s) into consideration for better quality of data.
4. The Project should continue to make efforts to establish the mass production system of human MAb against dengue virus using plant biotechnology during and even after the Project period in order to reduce its production costs.
5. The Project should make much more effort to make available the opportunities for many researchers to get some knowledge from the participants who had training in Japan.
6. Since most of the instruments possess high functional versatility, Thai researchers, especially for young researchers, should continue to study and work on research activities with enthusiasm so that they can proceed toward more advanced researches and/or applied researches from the view point of better technical sustainability.

### 3-7 Lessons Learnt

1. It can't be guaranteed that compounds with excellent efficacy and safety be obtained within a given period from the aspect of the nature of the researching approach, i.e., 'Screening and Identification', even though research activities were conducted in accordance with the research plan. Therefore, JICA should take this aspect into consideration when they conduct review and/or evaluation work under the scheme of SATREPS.
2. Since many institutes and subordinating laboratories were involved even in a single research subject, the Project has been paid closer attention to liaison and coordination amongst players for better project management. In addition to this, the dispatch plan of the Chief Advisor and short-term experts were well planned by taking the regular meeting opportunities such as working group meetings and scientific meetings. These efforts have contributed to the efficient operation of the Project.



3-8 State of the follow-up

None.