

## **Executive Summary**

### **Report of Activities and Outputs Generated from Chiang Mai University and the Université François-Rabelais de TOURS Collaboration Under the 2<sup>nd</sup> Frame Agreement of Cooperation 2008-2013**

Referred to the success of previous collaborative activities under the 1<sup>st</sup> Frame Agreement of Cooperation between Chiang Mai University, Faculty of Associated Medical Sciences (AMS) and the Université François-Rabelais de TOURS (2003-2008) and the Franco-Thai Collaborative Program in Higher Education and Research (2005-2008) entitled "Optimizing the Prevention of Mother to Child Transmission of HIV and the Care for HIV Infected Infants and Adults in Thailand", the continuous research and academic cooperative activities were performed under the 2<sup>nd</sup> Frame Agreement in 2008-2013.

The Faculty of Associated Medical Sciences, the François-Rabelais University and PHPT-IRD 174 collaboration is outstanding in its integration of research, education and capacity building of future health care providers. Those research and academic cooperative activities under the 2<sup>nd</sup> Frame agreement and with the IRD-UMI 174/PHPT collaboration are summarized as following;

**1. Ph.D. Research under the Co-Directed Thesis Convention for  
Mr. Woottichai Kanduang (Ph.D. in Biomedical Science and Doctorat  
Sciences de la Vie et de la Santé)**

**Title of research:** Genetic Analysis of Hepatitis B Virus (HBV) Mutants in  
HBV/HIV-1 Co-infected Patients in Thailand

**Research Grant:** The Agence Nationale de Recherches sur le Sida et les  
hépatites virales (ANRS); ANRS12179

**Collaboration:**

Tours University:	Prof.Dr. Alain Goudeau and Dr. Catherine Gaudy-Graffin
Chiang Mai University:	Dr. Wasna Sirirungsi and Dr. Satawat Thongsawat
IRD-UMI 174/PHPT:	Dr. Gonzague Jourdain and Dr. Nicole Ngo-Giang-Huong

## **Activities and Outputs:**

### **I. International/ National presentation**

1. Khamduang W, Sirirungsi W, Jourdain G, Leurent B, McIntosh K, Pagdi K, Somsamai R, Sirinontakan S, Hinjiranandana T, Ardong W, Lallemand M, Ngo-Giang-Huong N. Risk factors for Human Cytomegalovirus (HCMV) infection in infants born to HIV-1 infected mothers in Thailand. 4<sup>th</sup> Dominique Dormont International Conference, Maternal chronic viral infections transmitted to the infants: from mechanisms to prevention and care, 13-15<sup>th</sup> December, 2007, *Retrovirology* 2008; 5 ( Suppl.1):O12.
2. Khamduang W, Gaudy-Graffin C, Moreau A, Ngo-Giang-Huong N, Jourdain G, Lallemand M, Pipatnakulchai S, Putiyanun C, Kunkongkapan S, Wannarit P, Sirinontakan S, Ardong W, Sirirungsi W, Goudeau A. Transmission of Hepatitis B virus (HBV) minor variants in children born to HBV/HIV co-infected mothers. 5<sup>th</sup> Dominique Dormont International Conference, Mother-to-child transmitted viral diseases: from transmission to children care, 26-28<sup>th</sup> March, 2009, Paris, France, *Retrovirology* 2009; 6 ( Suppl.1):O9
3. Ngo-Giang-Huong N, Decker L, Sirirungsi W, Le Coeur S, Jourdain G, Khamduang W, Kanjanavanit S, Matanasaravoot W, Putiyanun C, Barin F, Lallemand M. Risk factors for HCV infection in HIV positive pregnant women and rate of HCV perinatal transmission in Thailand. 5<sup>th</sup> Dominique Dormont International Conference, Mother-to-child transmitted viral diseases: from transmission to children care, 26-28<sup>th</sup> March, 2009, Paris, France. (O15)
4. Khamduang W, Gaudy-Graffin C, Moreau A, Ngo-Giang-Huong N, Jourdain G, Lallemand M, Pipatnakulchai S, Putiyanun C, Kunkongkapan S, Wannarit P, Sirinontakan S, Ardong W, Sirirungsi W, Goudeau A. Hepatitis B virus (HBV) virological response to combination antiretroviral treatment includes lamivudine (3TC) in HIV/HBV co-infected individuals in Thailand. 10<sup>ème</sup> réunion du Réseau National Hépatites de l'ANRS, 21<sup>st</sup> - 22<sup>nd</sup> January, 2010, Paris, France.
5. Khamduang W, Jourdain G, Sirirungsi W, Layangool P, Kanjanavanit S, Krittigamas P, Pagdi K, Somsamai R, Sirinontakan S, Hinjiranandana T, Ardong W, Hongsiwong S, Nanta S, Borkird T, Lallemand M, McIntosh K, Ngo-Giang-Huong N for the Program for HIV Prevention and Treatment (PHPT). The interrelated transmission of HIV-1 and cytomegalovirus during gestation and delivery in the offspring of HIV-infected mothers. 18<sup>th</sup> conference on retroviruses and opportunistic infections (CROI), 27<sup>th</sup> February – 2<sup>nd</sup> March, 2011, Boston, Massachusetts, USA. (122).
6. Khamduang W, Ngo-Giang-Huong N, Jourdain G, Sirirungsi W, Le Coeur S, Sirinontakan S, Somsamai R, Pagdi K, Hemvuttiaphan J, Sukrakanchana P, Lallemand M. Human Immunodeficiency Virus-Hepatitis C Virus co-infection in pregnant women and perinatal transmission to infants in Thailand. The 13<sup>th</sup>

Thai national AIDS seminar, 29<sup>th</sup> – 31<sup>st</sup> March, 2011, Bangkok, Thailand. (AO8)

7. Khamduang W, Ngo-Giang-Huong N, Sirirungsi W, Chanta C, Karnchanamayul W, Ngampiyaskul C, Sirithadthamrong C, Hongsiriwon S, Kamonpakorn N, Watanayothin S, Jourdain G. Prevalence of hepatitis B virus (HBV) infection in infants born to HIV/HBV co-infected women and factors associated with vertical transmission of HBV. The 4<sup>th</sup> International Workshop on HIV Pediatrics. 20 – 21<sup>st</sup> July 2012, Washington DC, USA. *Reviews in Antiviral therapy & Infectious Diseases* 2013, 8: 20: O18
8. Sirirungsi W, Samleerat T, Ngo-Giang-Huong N, Collins I, Khamduang W, Caritey BD, Le coeur S, Pusamang A, Leechanachai P. Thailand National Program for early HIV diagnosis: six-year experience using real-time DNA PCR on dried blood spots. The 5<sup>th</sup> International Workshop on HIV Pediatrics. 28 – 29 June 2013, Kuala Lumpur, Malaysia. *Reviews in Antiviral therapy & Infectious Diseases* 2013, 7: 19: O\_16

## II. Publications:

1. Khamduang W, Gaudy-Graffin C, Ngo-Giang-Huong N, Jourdain G, Moreau A, Luekamlung N, Halue G, Buranawanitchakorn Y, Kunkongkapan S, Buranabanasatean S, Lallemand M, Sirirungsi W, Goudeau A; Program for HIV Prevention and Treatment Study Group. Long-Term Hepatitis B Virus (HBV) Response to Lamivudine-Containing Highly Active Antiretroviral Therapy in HIV-HBV Co-Infected Patients in Thailand. *PLoS One*. 2012;7(7):e42184. Epub 2012 Jul 31. (Impact Factor = 4.092)
2. Khamduang W, Ngo-Giang-Huong N, Gaudy-Graffin C, Jourdain G, Suwan kornsakul W, Jarupanich T, Chalermopolprapa V, Nanta S, Puarattana-Aroonkorn N, Tonmat S, Lallemand M, Goudeau A, Sirirungsi W; Program for HIV Prevention and Treatment (PHPT-2) group. Prevalence, risk factors and impact of isolated antibody to hepatitis B core antigen and occult HBV infection in HIV-1 infected pregnant women. *Clin Infect Dis*. 2013 Jun;56(12):1704-12. doi: 10.1093/cid/cit166. Epub 2013 Mar 13. (Impact Factor = 9.154)
3. Khamduang W, Gaudy-Graffin C, Ngo-Giang-Huong N, Jourdain G, Moreau A, Luekamlung N, Halue G, Buranawanitchakorn Y, Kunkongkapan S, Buranabanasatean S, Lallemand M, Sirirungsi W, Goudeau A, for the Program for HIV Prevention and Treatment (PHPT) study group. Analysis of residual perinatal transmission of hepatitis B virus (HBV) and of genetic variants in human immunodeficiency virus and HBV co-infected women and their offspring. *J Clin Virol*. Oct 2013; 58(2): 10.1016/j.jcv.2013.06.025. (Impact Factor = 3.287)

**Dr. Woottichai Kanduang** is now working as a Permanent Teaching Staff at the Division of Clinical Microbiology, Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University.

## **2. Collaborative Ph.D. Research for Ms. Sayamon Hongjaisee**

**Title of research:** Development of Assays to Determine Coreceptor Usage and Study of Molecular Determinants of HIV-1 CRF01\_AE Coreceptor Switching.

**Research Grants:** 1). Franco-Thai Cooperative Program for Higher Education and Research (Thailand Ministry of Education and French Ministry of Foreign Affair), 2009-2010.

2). The National Research University Project under Thailand's Office of the Higher Education Commission, 2011-2013.

3). Program of Excellence for Education and Research in South Countries (PEERS), 2014.

### **Collaboration:**

Tours University:	Prof. Dr. Francis Barin and Dr. Martine Braibant
Chiang Mai University:	Dr. Tanawan Samleerat
IRD-UMI 174/PHPT:	Dr. Gonzague Jourdain and Dr. Nicole Ngo-Giang-Huong

### **Activities:**

#### **I. International/ National presentation**

1. Hongjaisee S, Braibant M, Barin F, Ngo-Giang-Huong N, Sirirungsi S, Samleerat T. Evaluation of Genotypic Predictors for Prediction of HIV-1 Coreceptor Usage Compared with Phenotypic Assay in Thai Clinical Samples. The 1st Asian Conference on Hepatitis B and C, HIV and Influenza from basic science to clinical practice. Poster presentation. Beijing, China. 18-19 May 2012.
2. Shoombuatong W, Hongjaisee S, Barin F, Chaijaruwanich J, Samleerat T. HIV-1 CRF01\_AE Coreceptor Usage Prediction using Kernel Methods based Logistic Model Trees. RGJ Seminar Series LXXXIX Molecular mechanisms and technology developments in biomedical researches. Oral presentation. Chiangmai, Thailand. 31 August 2012.

3. Hongjaisee S, Shoombuatong W, Chaijaruwanich J, Braibant M, Barin F, Ngo-Giang-Huong N, Sirirungsi W, Samleerat T. Development of phenotypic and genotypic assay for determination of HIV-1 coreceptor usage in Thai clinical samples. The Second Thailand National Research Universities Summit: NRU SUMMIT II. Poster presentation. Bangkok, Thailand. 7-8 May 2013.
4. Hongjaisee S, Shoombuatong W, Chaijaruwanich J, Braibant M, Barin F, Ngo-Giang-Huong N, Sirirungsi W, Samleerat T. A simple and suitable assay for determination of HIV-1 coreceptor usage in CRF01\_AE subtype. The 11th International Congress on AIDS in Asia and the Pacific (ICAAP11). Poster presentation. Bangkok, Thailand. 18-22 November 2013.

## II. Publication:

Shoombuatong W, Hongjaisee S, Barin F, Chaijaruwanich J, Samleerat T. HIV-1 CRF01\_AE coreceptor usage prediction using kernel methods based logistic model trees. *Comput Biol Med* 2012; 42: 885-9. (Impact Factor = 1.359 )

**Ms. Sayamon Hongjaisee** is now conducting her final part of Ph.D. research at INSERM U966, Faculté de Medecine, Université Francois Rabelais, Tours, France under the supervision of Prof. Francis Barin (June-November 2014).

## 3. Collaborative project supported by the Program of Excellence for Education and Research in South countries (PEERS)

The collaborative project entitled “**Neutralization of HIV, HBV and HCV by antibodies in the mother-to-child transmission context: lessons for vaccine efficacy**” has been supported by the Program of Excellence for Education and Research in South countries (PEERS) during 2013-2014.

### Collaboration:

Tours University:	Prof. Dr. Alain Goudeau, Prof.Dr. Francis Barin, Dr. Catherine Gaudy-Graffin, Dr. Martine Braibant
Chiang Mai University:	Dr. Wasna Sirirungsi, Dr. Tanawan Samleerat, Dr. Wootichai Khamduang
IRD-UMI 174/PHPT:	Dr. Gonzague Jourdain and Dr. Nicole Ngo-Giang-Huong

Summary of collaborative activities in 2013 are as followings;

### **Research activities:**

**Project 1.** *Hepatitis B vaccine failure in offspring of women co-infected with human immunodeficiency virus and hepatitis B virus in Thailand.*

This work was initiated in the context of a long-lasting Franco-Thai collaboration between Chiang Mai University and the François-Rabelais University. The aim of the study was to evaluate the potential of vaccine-induced anti-HBsAg antibody to neutralize such HBV mutants.

Under a support of the PEERS project, Dr. Woottichai Khamduang was able to have a long-duration stay in France (March 14 – September 7, 2013). During this stay under the supervision of Pr. A. Goudeau and Dr. C. Gaudy-Graffin, Dr. W. Khamduang conducted *in vitro* studies with the support of Dr. C. Sureau (National Institute for Blood Transfusion), one of the international leaders in this domain.

**Output:** Using the production of HBV pseudoviral particles and *in vitro* neutralization assay, we were able to precisely demonstrate the effect of HBV mutations on HBV infectivity capacity and its sensitivity to the neutralization activity of vaccine-induced antibodies.

This part of the project offered the opportunity for Dr. Woottichai Khamduang to complete his previous studies and to acquire skills on pseudotyped virus technology to conduct future studies independently in Thailand or in Tours. A manuscript based on this study is currently in preparation.

**Project 2.** *Dynamics of variants during HCV transmission and role of neutralizing antibodies: analysis in the context of mother-to-child transmission.*

About 3% of the world's population has been infected with Hepatitis C virus (HCV). Primary infection is usually asymptomatic but 70% of infections evolve to chronic hepatitis leading to cirrhosis and hepatocellular carcinoma.

We propose to identify molecular determinants associated with a stronger capacity of maternal HCV viral variants to be transmitted to their newborn. The role of neutralizing antibodies in the selection process will also be investigated using pseudotyped virus technology. Using a very sensitive technology, we will identify the most representative HCV variants, infecting each mother and infant pair. The results of this study will provide new insights into the selective process occurring during HCV transmission.

Support for this project was submitted to the Thrasher Foundation in October 2013. Unfortunately, the financial support was not accorded, considering that the project was interesting for basic research but without short-time downstream application in public

health. Although we agree with this comment, we still believe that the basic research deserves to be done and will be useful in a near future. A funding for this project was recently obtained from the region Centre (108 000 Euros), as well as a 3 years scholarship for a PhD student (Thibault Guinoiseau, that obtained his Master degree in June 2014). This project will start at the end of September 2014.

### **Experts visit to Chiang Mai University and staff/student training in Tours in 2013:**

- Long-term visit of Dr. W. Khamduang for training and experiments using the in vitro HDV/HepaRG system. Tours-Paris, March-September 2013
- Short-term visit of Dr C Gaudy-Graffin, Chiang Mai, September 7-15, 2013.
  - o Contribution to the symposium: "Research for Primary and Secondary Prevention of HIV Associated Infections and Cancers in South East Asia".
    - Plenary session: "Importance of virological markers for clinical management of HCV infection: HCV diagnosis, quantification and genotyping".
    - Training course (clinical cases): "Virological markers for clinical management of HCV infection".
  - o Seminar for Master students, Faculty of Associated Medical Sciences: "Hepatitis C virus (HCV): structure, natural history, importance of virological markers for clinical management".
  - o Working sessions at IRD UMI174/PHPT and Faculty of Associated Medical Sciences: discussions, analysis of the available biological material and proposals for the HCV project.
- Short-term visit of Prof.Dr. F. Barin and Dr. M. Braibant, Chiang Mai, December 1-5, 2013.
  - o Seminar for Master students and researchers, Faculty of Associated Medical Sciences.
    - Prof.Dr. F. Barin: "Neutralizing antibodies in HIV infection role, recent developments and perspectives for immunoprophylactic and immunotherapeutic interventions".
    - Dr. M. Braibant: "Evidence for a continuous drift of the HIV-1 species towards higher resistance to neutralizing antibodies over the course of the epidemic".

#### **4. Establishment of the International Master's program within the ERASMUS plus (former ERASMUS Mundus) initiative**

Regarding an initiative of the Université Francois Rabelais de Tours to establish an international Master's program based on Master program in infectiology ("Infectiologie Cellulaire et Moléculaire, Vaccinologie, Anticorps Thérapeutiques"), Faculty of Associated Medical Sciences, Chiang Mai University agrees to take part in this program as an Associated-partner.

At the moment, process of including more European partner institutes is ongoing while the Roslin Institute, Edinburgh, United Kingdom has accepted to be a Full-partner and the Institute of Biochemistry, Bucharest, Romania and McGill University, Montreal, Canada have accepted to be an Associated-partners.

The proposal for establishment of an International Master's program is planned to apply to the Erasmus+ in March 2015.