



- 17. Sentinel Human Surveillance for Influenza in Thailand  
**Status:** New protocol approved by Thai MOPH IRB. Site initiation at Kwai River Mission Hospital in Sangkhlaburi planned for March 2012.
- 18. Tafenoquine Prophylaxis Phase 3 Trial in Cambodia  
**Status:** Protocol development.

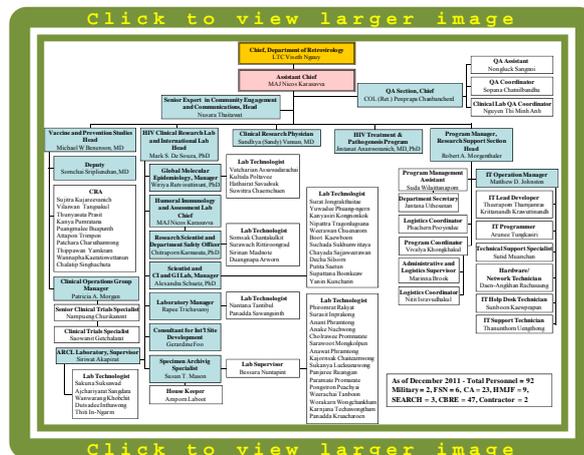
## DEPARTMENT OF RETROVIROLOGY

### DEPARTMENT MISSION

The mission of the Department of Retrovirology is to prepare for and conduct advanced development of preventive HIV vaccines for soldiers. This mission is achieved collaboratively and supported through i) the performance of preclinical and clinical (phase I-III) trials of candidate vaccines and their evaluations for safety, immunogenicity and efficacy, ii) the identification and characterization of potential cohorts for phase III vaccine trials, iii) the establishment of diagnostic assays which differentiate infection from vaccine-induced immune responses, iv) the characterization of HIV viruses circulating in the region, and v) the determination of the natural history of HIV infection and disease in local populations.

### PERSONNEL

The Department of Retrovirology consists of 87 staff that includes 2 Active-Duty Army Officers (1 Medical Corps, 1 Medical Service Corps). The department employs contracted employees and Thai nationals with MDs and PhDs to conduct its mission. An overview of the organization chart is provided below as well as listing of each departmental staff member. The Department of Retrovirology has added personnel due to continuation of two successful MIDRP, NIAID, and Advance Development funded activities and increased laboratory work load and the initiation of three upcoming HIV vaccine trials as a follow on to the successful RV144 study.





## IN-HOUSE TRAINING PROGRAMS AND OUTSIDE TRAINING OF PERSONNEL

### **In-House Training Programs Provided by AFRIMS:**

- Routine Safety and Occupational Health Training
- Fire Prevention, Protection, Report and Investigation
- Accident Illness and Complaints Reporting, Records and Investigations
- Harzard Communication Program
- Routine Prophylaxis and Screening
- Biosafety in Laboratory
- Laboratory Waste Management
- Chemical Safety
- Safety Equipments Usage
- Bloodborne Pathogens Exposure Control Plan
- Respiratory Protection Program
- Post-exposure Prophylaxis and Intervention

### **In-House Training Programs Provided by or to the Department Laboratories**

- Gut Biopsy Update Meeting. Division of Gastroenterology, Chulalongkorn University, Bangkok, Thailand. January 2011.
- Stakeholder Consultations on CAB Constitution and Capacity Building in Clinical Research, LTC Ngauy, Dr. Somchai Sriplienchan, and Ms. Nusara Thaitawat. Department of Retrovirology, Bangkok, and All Seasons Pattaya, Thailand. 2 February, 2 March, 13 May and 22-24 July 2011.
- HIV Testing and Monitoring and Quality Assurance for Vietnam PEPFAR Clinical Laboratory QA Coordinator, Retro-QUA and laboratory staff, Retrovirology Department, AFRIMS, Bangkok, Thailand. March 2011.
- Cell Transfection and Protein Purification Training, HI laboratory, AFRIMS, Thailand. April 2011.
- COBAS TaqMan HIV-1 Test Training, Ms. Panyaporn Rungruangsrisk. Roche Diagnostic (Thailand) Ltd., MOL laboratory, AFRIMS, Thailand. June 2011.
- MHABce Genotyping Procedure Training to Ms. Suwittra Chaemchuen. MERL Laboratory, Bangkok, Thailand. June 2011.
- Phylogenetic Analysis, Dr. Morgane Rolland. MHRP, MERL laboratory. September 2011.
- Annual Refresher for NGO Partners (RV217 Protocol Training and Capacity Building in Clinical Research), Dr. Somchai Sriplienchan, Ms. Nusara Thaitawat, Ms. Patchara Charuthamrong and Ms. Thunyasuta Prasit. All Seasons Pattaya, Thailand. August 2011.
- Training in Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials, Clinical Operations Group and RTA-AFRIMS teams. Montien Hotel, Pattaya, Thailand. August 2011.
- RF and Whole Blood ADCC Assay Training, Ms. Leia Wren, Ph.D. student, Australia. CI Laboratory, AFRIMS, Thailand. September-October 2011.
- APTIMA Combo 2 Assay Training, MOL staff, MERL Laboratory, Thai Red Cross, Thailand, October, 2011
- Consultancy to Other MHRP International Laboratories on Aptima, HIV-1 Trugene (HIV Resistance testing) and TaqMan Assay Performance and Data Compilation.



### Outside Training

- Initial Team Member Training, on-line, <http://education.cap.org>. March 2011.
- Voluntary Confidential Counseling and Testing and Protocol Training, co-hosted with the Foundation for Service Workers in Group (SWING). Erawan Camelot Hotel, Pattaya, Thailand. March, 2011.
  - Quality Management for Medical Laboratory, CDC. Intercontinental Hotel, Bangkok, Thailand. March 2011.
  - HIV Evolution, Genomics and Pathogenesis. Whistler, Canada. March 2011.
  - The 13<sup>th</sup> National AIDS Conference. MoPH, Muang Thong Thani, Bangkok, Thailand. March 2011.
  - The 35<sup>th</sup> Thailand Medical Technology Society Annual Meeting, Thailand Medical Technology Society. Sunee Grand Hotel, Ubonratchathani, Thailand. April 2011.
  - HIV Full-Genome PCR, Sequencing, and Analysis Training. Rockville, U.S.A. April-May 2011.
    - Public lecture series (1): “Updates Antiretroviral Treatments” by Dr. Somsit Tansupawadikul (Bamrasnaradura Hospital), and “Hormones and ARVs” by Dr. Ake-Jittra (Thai-U.S. Collaboration in Public Health), co-hosted with the Health and Opportunity Network. Montien Hotel Pattaya, Thailand. May 2011.
    - How to Engage Hard-to-Reach Populations by Rayong STI teams from the Provincial Chief Medical Office and Community Hospitals, ECHO Center. Pattaya, Thailand. June 2011.
    - Annual Radiation Safety Training, Office of Atoms for Peace (OAEP). Bangkok, Thailand. June 2011.
    - Training of Trainers in Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials, AVAC, TNCA. Windsor Hotel, Bangkok, Thailand. July, 2011.
    - HIV and Flow Cytometry Meeting. Petchaburi, Thailand. July 2011.
    - The 3<sup>rd</sup> Vaccine Conference, MoPH. Windsor Suites Hotel, Bangkok, Thailand. July 2011.
      - HON Members’ Retreat. Rayong, Thailand. July 2011.
      - Validation to Help Meet and Mitigate Regulatory Risk While Balancing Your Business Requirements by Applied Biosystems. JW Marriott Hotel, Bangkok, Thailand. August 2011.
      - The 10<sup>th</sup> International Congress on AIDS in Asia and the Pacific (ICAAP). BEXCO, Busan, Republic of Korea. August 2011.
      - Essentials of GCP for the New Coming Investigator, Royal Thai Army Medical Department. Phramongkutklao Hospital, Bangkok, Thailand. August 2011.
      - Community Satellite “Moving Forward Together” at AIDS Vaccine 2011 Conference. Bangkok Convention Center, Bangkok, Thailand. September 2011.
      - AIDS Vaccine 2011 Conference. Bangkok Convention Centre, Bangkok, Thailand. September 2011.
        - MHRP-MoPH RV144 Immune Correlated Briefing. Thai MoPH. Siam City Hotel, Bangkok, Thailand. September 2011.
        - Public lecture series (2): “Community Health and Participatory Practice” by Mr. Steven Wakefield (HVTN), Co-hosted with the Pattaya Municipality. City Hall, Pattaya, Thailand. September 2011.
        - Clinical Pathology Network 2011: Current and Future Trends, Clinical Pathology Institute of Phramongkutklao Hospital. Phramongkutklao Hospital, Bangkok, Thailand. November 2011.



- World AIDS Day 2011. Walking Street, Pattaya, Thailand. 1 December 2011.
- CAVD Meeting. Seattle, U.S.A. December 2011.
- Cold Chain Training, Retro-QAU. Bang Lamung, Thailand. December 2011.

## ACCOMPLISHMENTS

The Department successfully maintains the College of American Pathologist accreditation for the clinical laboratories. With the completion of the world's largest phase III HIV vaccine trial conducted on the Eastern seaboard of Thailand (Chon Buri and Rayong Provinces) and the publication of the efficacy result in 2009, the protocol team's effort in 2010 shifted to laboratory analysis. In particular, efforts to characterize the HIV-1 viruses that caused infections and standard immunological analysis to determine what caused the protective effects (correlates of protection) of the vaccine regimen and well qualified assays using a case-control design. The results from these intensive laboratory efforts and multi-center and multi-national collaborations were presented at the AIDS vaccine Meeting 2011 in Bangkok, Thailand. Two papers have been submitted for publication detailing the results of this work.

Ongoing activities in 2011 include the development of three intensely immune based clinical studies to extend and build on the modest success of RV144. Results suggest that the vaccine regimen protected people at lower risk of infection, and the protection appeared to wane over time. One proposed study involves boosting some of the volunteers from RV144 to see if this will extend and increase the immune response (a "boost" is an additional vaccine dose given after the primary doses to increase the immune response to the original vaccine antigens). This study is anticipated to start the beginning of FY12.

Another study, anticipated to start in the end of FY12 will recruit several hundred new volunteers in Thailand who will receive a similar vaccine regimen as in RV144, plus an additional boost at 12 months. This study would provide insight into the benefit of the additional boost and collect more blood and some mucosal tissue samples so that extensive research can be conducted on the study participants' immune responses.

The third study is smaller and will intensively interrogate the system and mucosal immune response to the protein only component of the RV144 prime boost regimen (AIDSVAX) to determine if the combination contributed to the success of RV144. It will serve as a comparator for the other 2 studies.

A study of breakthrough infections in the Phase III trial which began in May 2006 closed to enrollment in June 2009 with the completion of RV144. The study was closed to enrollment in May 2011 and data resulting from breakthrough infection cohort study was presented at the AIDS Vaccine Meeting in 2011. Briefly, the vaccine showed no long term effect (3 years of follow up) on clinical progression as determined by effect on CD4 and occurrence of AIDS defining illness. It had no effect on viral load. This result is consistent with RV144. Of note, vaccine recipients did appear to have a statistically lower viral load in semen compared to placebo recipients. This result is promising and influences future interest and focus on immune response on the mucosal compartment.

A phase 1 study evaluating a novel prime boost DNA/MVA-CMDR vaccine candidate conducted in Rockville, MD and East Africa (Kenya, Uganda, and Tanzania). This study evolved from a prior Phase 1 study conducted in Rockville, MD and Thailand evaluating only the MVA-CMDR product given in three doses using two delivery methods (IM vs. ID). The Department of Retrovirology will be conducting the laboratory immuno-monitoring and exploratory work on the mucosal immune response to vaccination.



In collaboration with the University of Hawaii and the Thai Red Cross AIDS Research Centre (SEARCH – Southeast Asia Research Collaboration with Hawaii), the Department is currently working on several protocols. One is an exploratory cohort study in which HIV-positive individuals with and without dementia are studied to determine host factors that may contribute to the development of AIDS associated dementia. This study is has enrolled approximately 50 of 60 volunteers and preliminary data is being analyzed.

Another collaborative study with SEARCH and the Thai Red Cross investigated the incidence, demographics, HIV subtype and genotypic resistance in acute HIV infection within a high-risk Thai cohort at the Thai Red Cross Anonymous Clinic, which has an HIV prevalence of about 17%. TRCAC uses 4<sup>th</sup> generation enzyme-linked immunoassay (AxSYM) for HIV diagnosis. AxSYM-negative samples are pooled to detect acute HIV infection by nucleic acid testing (NAT). Acute HIV infection samples were AxSYM-negative, NAT positive. Additional acute HIV infections were identified if the sample is AxSYM and NAT positive by differential reactivity on third and/or second generation e EIA. Demographic and risk behavior data from the TRCAC questionnaires were collected.

As of January 2012, approximately 45,000 samples have been screened, 76 acute infections confirmed and 64 volunteers are enrolled in the protocol. The majority (97%) of volunteers elected to start ART and a large number (70%) agreed to undergo invasive procedures. Volunteers are mainly young MSMs and are infected with CRF01\_AE, R5 tropic virus predominately identified in Fiebig 1 (22 subjects), Fiebig 2 (n = 9), and Fiebig 3 (n = 26).

A manuscript has been submitted for publication. Key findings to be reported are:

- Mega-HAART in early Fiebig stage AHI may prevent CD4 depletion of the sigmoid colon, and render gut and peripheral HIV RNA undetectable.
- Mega-HAART may reduce viral burden and promote mucosal immune restoration, indicated by the increased frequency of CD4+CCR5+ T cells in the sigmoid colon and could be a crucial component of a functional cure.
- Mega-HAART may decrease the viral in semen more rapidly that standard HAART.
- Total and Integrated HIV DNA in the sigmoid colon declined significantly after Mega-HAART.

The protocol has been amended to increase enrollment to 100 and to allow data sharing with the study of another acute infection cohort in Pattaya. Results from this study will need to be compared to HIV-negative individuals and chronically infected individuals so another protocol was developed that will allow sigmoid bx, leukapheresis, and CSF collection for comparison.

Protocol entitled “Assessment of neutralizing antibody (NAb) in participants from phase I/II Trials of ALVAC-HIV (vCP1521) priming with Chiron gp120 B/E, Sanofi-Pasteur oligomeric gp160, or AIDSVAX™ B/E gp120 B/E boosting against a newly developed, standardized panel of HIV-1 isolates”. This study aims to use the TZM-bl cell line Luciferase Reporter Pseudovirus NAb assay method. It will also aim to use archived plasma samples from previous phase I/II prime-boost HIV vaccine studies. The objectives of this protocol are i) to compare cross-clade NABs among samples from HIV uninfected volunteers who have received prime-boost regimens of ALVAC vCP1521 and three different Env subunit protein boosts, ii) to compare the frequency and titers of NABs induced among the three protein boost regimens, and iii) to evaluate the evolution of NAB; i.e., the change in immunogenic responses whether NAB is detectable and/or shows variation in its expression, among volunteers during the prime-boost regimen. Work from this protocol aided in the correlates work for RV144. In 2011, more strains of pseudoviruses were available for TZM-bl luciferase neutralizing antibody assay with samples



from the earlier phase 3 studies in order to study dose effectiveness to neutralizing antibody activities. Two manuscripts related to this work were completed. In the coming year, a new platform used in neutralizing antibody assay will be added along side with the TZM-bl platform. This will enhance the sensitivity of the detection of neutralizing antibodies particularly in vaccine studies. Samples will be assayed using A3R5 cell line, the results will be compared to those from TZM-bl cell line.

A multi-site cohort study was designed to define risk behaviour, incidence of HIV in high-risk populations (MSMs, SWs, and TGs) and to identify individuals with acute HIV infection to support the full characterization of host response and viral dynamics in HIV pathogenesis. Volunteers are enrolled and followed for two years with blood collection every 6 months after baseline studies. Alternating 6 months the volunteers receives counseling and HIV prevention education. Twice a week the volunteers provide a capillary blood specimen for sensitive testing of very early HIV infection. Those identified as recently infected are studied intensively for ten visits and then followed for an additional 5 years.

The protocol began in July 2009. More than 1,313 potential volunteers have been interviewed and 628 volunteers have taken the ACASI questionnaire. Six hundred two volunteers passed the screening visit and 454 were successfully enrolled. Eighty-nine potential volunteers were HIV infected at baseline, for an overall prevalence of 14.5% (MSM 19.9%, FSW 1.3%, TGs 17.8%). Twenty-six incident cases have been detected for an overall incidence rate of 5.1/100 person years. Among MSM and TGs the incidence rate is 6.9/100 person years. Eighteen of the infected volunteers were captured during the very early stages of HIV infection (Fiebig stages I or II). Retention to the large blood draw visits and to finger stick small blood volume (twice weekly collections) has been approximately 75%. Enrollment will continue until 500 volunteers have begun the small blood volume collections. A modification to the protocol is in process which will incorporate vaginal and rectal swab collections and two questionnaires, a receptive risk questionnaire, and a genital cleansing questionnaire.

In the area of community engagement, a Community Advisory Board (Retro CAB) was formed in July 2011. The Department is piloting the UNAIDS-AVAC Good Participatory Practice guidelines for biomedical HIV prevention trials with the view to implement these practices in all its future protocols that involve human subjects. It has established strong ties with the local community and stakeholders in the study site in Pattaya, and a working relationship with national AIDS NGOs, particular the Thai NGO Coalition on AIDS. Its senior staff are regularly called up by NGOs to provide training or serve as resource persons in AIDS vaccine and biomedical HIV prevention research, clinical trials and bioethics.

## **COLLABORATIONS**

- Ministry of Public Health, Department of Disease Control (DDC), Nonthaburi
- Vaccine Trial Centre, Faculty of Tropical Medicine, Mahidol University, Bangkok
- Division of AIDS, NIAID, NIH
- Siriraj Hospital, Faculty of Medicine, Mahidol University, Bangkok
- AFRIMS- Division of Research (RTA component)
- Phramongkutklao Army Medical Center, Bangkok
- Data Management Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok
- The Thai Red Cross AIDS Research Centre
- Hawaii AIDS Clinical Research Program, John A. Burns School of Medicine, University of Hawaii



- Laboratory for AIDS Vaccine Research and Development, Duke University Medical Center, Durham, NC, U.S.A.
- Collaboration of AIDS Vaccine Discovery
- Comprehensive Antibody - Vaccine Immune Monitoring Consortium (CA-VIMC)
- Sanofi-Pasteur
- VaxGen, Inc. (now Global Solutions for Infectious Diseases)
- Thai NGO Coalition on AIDS (TNCA)
- The Health and Opportunity Network (HON)
- The Foundation for Service Workers in Group (SWING)

## **SUMMARY OF FUTURE PLANS AND STRATEGIES**

The immediate focus of the coming year is to start the three follow on studies to evaluate and perhaps improve the immunogenicity of the RV144 regimen. Evaluation and down-selection of HIV Env proteins for use in a phase 2B trial is being pursued and may include collaborations with the Gates Foundation and the Department of Veterinary Medicine at AFRIMS for NHP work. Due to the expanding work, capacity, and specimen repository requirements of the department in the upcoming years, additional laboratory, specimen processing, and repository space have been sought through the RTA Medical Department. A phase 2B trial is planned for FY16 to evaluate early efficacy of this vaccine regimen in community risk and high-risk (MSM) populations. In preparation of this phase 2B study, activities for development of cohort studies to characterized suitable populations will begin in FY13. These studies will involve new collaborators at Chiang Mai University.

The Department will continue to serve as one of the MHRP's major testing platforms for phase I-II studies of newer vaccine candidates which will involve further testing of the subtype E (CRF01\_AE) MVA vaccine candidate currently in phase I testing and newer DNA vaccine candidate. Further development of populations suitable for more advanced testing in phase 2B and 3 vaccine trials will be pursued through cohort studies of high-risk populations in Chiang Mai, Bangkok and Pattaya.

## **DEPARTMENT OF VETERINARY MEDICINE**

### **DEPARTMENT MISSION**

To protect military personnel and their families against tropical disease threats through pre-clinical product development of new prophylactic and therapeutic drugs and new or improved vaccines.

To fulfill this mission the Department of Veterinary Medicine (DVM) conducts biomedical research in animal models and zoonotic disease surveillance, provides veterinary expertise and research animals that are free of confounding diseases to intra- and extra-mural collaborators, and ensures that all animals receive humane, proper, and safe care and that the USAMC-AFRIMS' Animal Care and Use Program complies with appropriate laws, regulations and guidelines.