



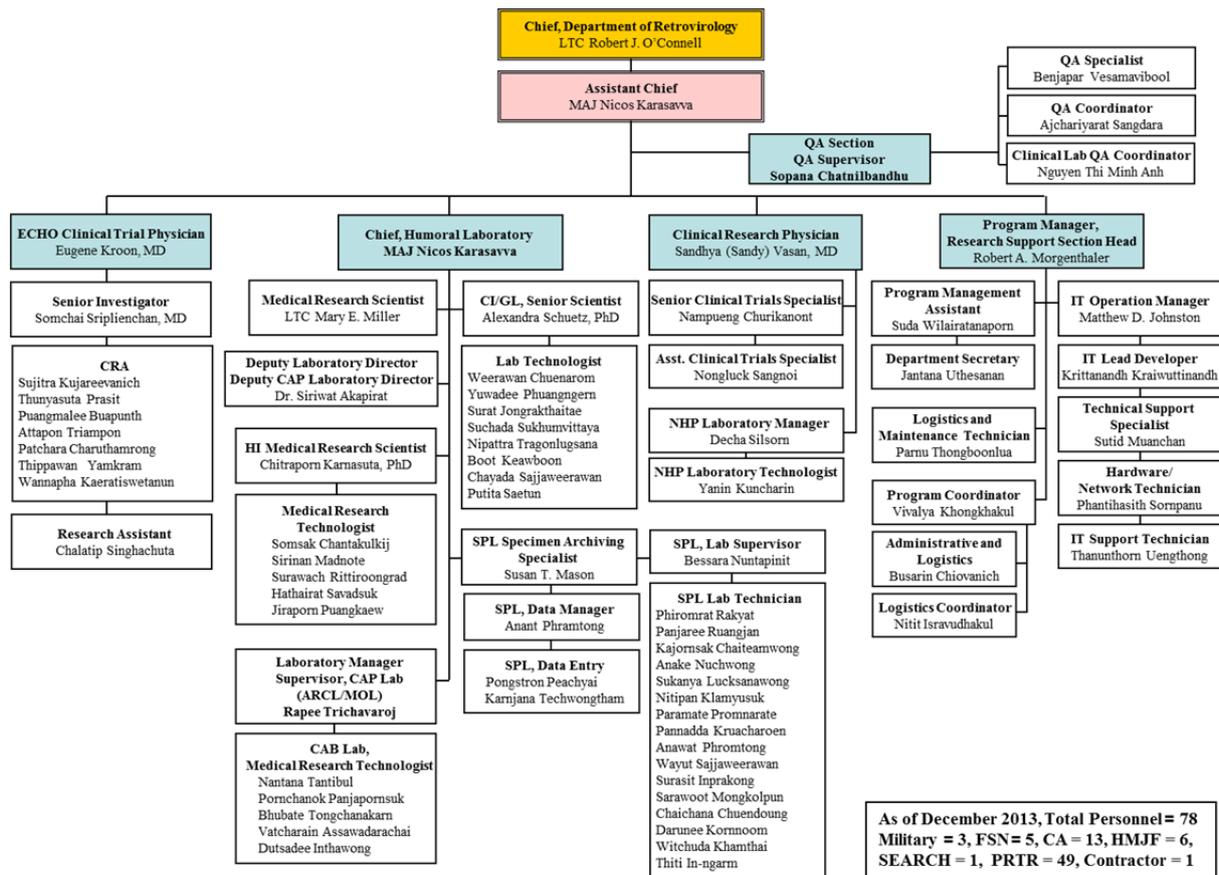
DEPARTMENT OF RETROVIROLOGY

MISSION

The mission of the Department of Retrovirology is to conduct activities to support the development of a safe and globally effective HIV vaccine. 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) coordination of product development activities required for efficacy assessment of modified HIV vaccine products, and iii) conduct of clinical studies and associated laboratory science to understand acute HIV infection and establish a platform for evaluation of interventions to cure HIV infection

PERSONNEL

The Department of Retrovirology consists of 76 staff that includes 3 Active-Duty Army Officers (1 Medical Corps, 2 Medical Service Corps). The department employs contracted employees and Thai nationals with a wide variety of skills 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 underwent a slight reduction in personnel due to a relative lull in clinical trial activity. Personnel increases are expected commensurate with an increase in advanced development vaccine clinical trials and acute infection cure intervention studies.





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
- Hazard 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
- Composite Risk Management
- Mandatory Ethics Training
- Computer User Training on “DoD Information Assurance Awareness Training”
- Mandatory EEO and Sexual Harassment Training
- Essential OHS Topic for Supervisors
- Requirement for Document Document and Amendment
- Animal Biosafety Level-3 (ABSL-3) Hazardous Training
- The Humane Care and Use of Lab Animals
- Institutional Biosafety Committee (IBC)
- Temperature Sensitive Medical Products (TSMP)

In-House Training

- The Operation and Maintenance of System Automated Hematology Analyzer XP-100. AFRIMS, Bangkok, Thailand. January 2013
- Privacy Act and HIPAA Operations Refresher. On-line Training. AFRIMS, Bangkok, Thailand. January 2013
- STIs Training for stakeholders and ECHO staff. Pattaya, Thailand. February 2013
- Human Subjects Protection (HSP) and Good Clinical Practice (GCP) Training, AFRIMS. Bangkok, June 2013
- Elucidating RV144’s Efficacy A Literature Review Focused on the Prostate by LTC Mary Miller, Department of Retrovirology. AFRIMS, Bangkok, Thailand. June 2013
- USAMMDA Human Subject Protection (HSP) and Good Clinical Practice (GCP) Introduction Training, by PPD U.S.A. AFRIMS, Bangkok, Thailand. 25 June 2013
- Cold Chain Management Awareness course (CCM Training) by World Courier. AFRIMS, Bangkok, Thailand. 4 October 2013
- Intermediate Medical Acquisition Course (IMAC). November 2013
- Thermo Scientific Training, Freezer -80°C Operator’s Training, Technical and Maintenance. Department of Retrovirology, AFRIMS, Bangkok, Thailand. 25 November 2013
- CITI Program Training on “Biomedical Research Support Staff”. On-line, <http://citiprogram.org>. November 2013

Outside Training

- Presentation of RV254 data on Th17 and Treg, CROI. Atlanta, USA. 3-6 March 2013
- Norman Letvin Mini Symposium. Harvard Medical School, Boston, Massachusetts, USA. 18-19 March 2013



- PMK-AFRIMS Research Collaborative Discussion: a Study in a Population at High Risk for HIV-in Pattaya by Dr. Somchai Sriplienchan. Pramongkutklo Hospital. 26 June 2013
- Thailand Laboratory Accreditation Forum 2013 "Thai MT Standard Global Sharing". Bangkok Thailand. 29-30 July 2013
- AIDS Vaccine: Presentation of RV305 immunogenicity data. Barcelona, Spain. 7-10 October 2013
- The Advance Workshop on QA/QC for HIV Testing for PEPFAR Vietnamese Military Hospital. Ho Chi Minh, Vietnam. 10-12 December 2013

ACCOMPLISHMENTS

The department successfully maintains the College of American Pathologist accreditation for the clinical laboratories. RV144 showed for the first time that candidate HIV vaccines, namely ALVAC-HIV and AIDSVAX B/E, can prevent HIV infection. This landmark study highlighted the successful collaboration between AFRIMS, the Thai Ministry of Public Health, and Mahidol University. The success of this study spurred a flurry of scientific and clinical activities within the department and among Thai and international collaborators, leading to the discovery of a potential correlate of protection that will help guide future vaccine development efforts.

The Department of Retrovirology's ability to conduct clinical trials meeting local and international regulatory standards is support by the its exemplary College of American Pathologist certified clinical laboratory, specimen processing and archiving laboratory, and its basic science research program. In the 10 years of its young existence, the department's administrative, laboratory, processing, and archiving facilities have been scattered between multiple locations in Bangkok and Chonburi. The completion of the RV144 study, the subsequent intensive immunologic analysis of the RV144 results, and the volume of specimens processed, collected, stored, and analyzed for the acute cohort studies rapidly outstripped the Department's physical space capacity. In order to consolidate operations and eliminate a logistically complex operation, AFRIMS, requested space from the RTA Surgeon General in 2010 to renovate the RTA Medical Depot warehouse to build a state of the art laboratory and archiving facility.

The opening of the HIV Vaccine Research Center of Excellence at the end of 2012 has been followed by completion of laboratory consolidation, which became fully realized in 2013. The HVRC consolidates the majority of the laboratory activities conducted by the Department of Retrovirology and the Royal Thai Army. Housed under the roof of the HVRC are the AFRIMS Clinical Research Lab (ARCL) and Molecular Lab to perform eligibility and safety labs for clinical trials. The humoral, cellular, and non-human primate labs are research laboratories established to interrogate the epidemiology and molecular characteristics of the HIV virus and to the host's cellular, humoral, and innate immune responses to natural infection and vaccine challenge. The largest section of the Center of Excellence is the specimen processing and archiving laboratory. They process all samples collected from clinical trials to include blood and mucosal secretions and provide archiving, monitoring, and storage for up to 100 freezers. The Department of Retrovirology shares this space with RTA Medical department. The RTA laboratories include a serology, veterinary medicine, histopathology, and processing laboratory.

Follow on work to build upon the success of RV144 resulted in the launch of RV305 at the Banglamung site in Chonburi, Thailand entitled "Randomized, Double Blind Evaluation of Late Boost Strategies for HIV-Uninfected Participants in the HIV Vaccine Efficacy Trial RV144: Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming with VaxGen gp120 B/E (AIDSVAX[®] B/E) Boosting in HIV-uninfected Thai Adults". The study opened in May 2012 and completed enrollment in December 2012, and completed all vaccinations by 2013. An interim immunogenicity analysis was conducted to establish continued immunogenicity of



the AIDSVAX B/E protein, which is more than 20 years old. This analysis demonstrated that the product remains immunogenic, raises binding and neutralizing antibodies at higher levels than RV144, and showed that ALVAC alone does not result in antibody responses. These results have directly informed the much larger RV306 study, providing reassurance that the study should still go forward, and causing an alteration in study design.

In 2013, the department launched a human vaccine clinical trial, RV306, entitled “Randomized, Double Blind Evaluation of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP1521) Priming and Multiple Boosting Regimens with and without VaxGen gp120 B/E (AIDSVAX[®] B/E) in HIV-uninfected Thai Adults”. In addition, the department anticipates initiation in 2014 of another clinical vaccine trial, RV328 entitled “Randomized, Double Blind Evaluation of Sequential Administrations of gp120 B/E (AIDSVAX[®] B/E) (GSID) with 1-Year Boosting in HIV-uninfected Thai Adults”.

In 2013, the department began development of a new HIV vaccine trial that will evaluate a novel adjuvant combination that is believed will result in higher and more durable anti-HIV antibody responses compared to the adjuvant used in the RV144 trial. The study is entitled, “Randomized, Double Blind Phase I Trial to Evaluate Sanofi Pasteur Live Recombinant ALVAC-HIV (vCP1521) and Global Solutions for Infectious Diseases (GSID) gp120 B/E (AIDSVAX[®] B/E) formulated in L(MPLA) and alum in a Prime-Boost Regimen in HIV-uninfected Adults in Thailand, Uganda and Mozambique”. The Department Chief will serve as protocol chair for this study.

The major product development obstacle barring further advancement of the RV144 vaccine regimen has been lack of a fully committed partner that would partner with existing committed stakeholders to provide vaccine manufacturing capability for the protein boost should the next planned efficacy trial be successful. Sanofi Pasteur, the developer of ALVAC-HIV prime portion of the RV144 regimen, has insisted that this partner cannot be them because they are already making enormous capital investments supporting ALVAC-HIV. Because none of the other large pharmaceutical vaccine manufacturers accepted our invitation to become partners, the department is working closely with the Military HIV Research Program to form a consortium to build protein vaccine capability under an effort titled “The AIDS Vaccine Efficacy Consortium (AVEC)-Thailand”. This effort brings together the U.S. government, Thai government, and any other parties interested in contributing to the effort, with the purpose of bringing their respective funding resources together to engineer a manufacturing capability to make an HIV protein boost or another product of interest to the Thai government. A noteworthy milestone of this effort was a one day Summit for an AIDS Free Generation in Thailand, during which strong support was voiced by The U.S. Ambassador to Thailand, The Minister of Health for Thailand, and a key advisor to the Minister of Science and Technology. In addition, in December, the department chief led a delegation of three members from each of the Ministries of Health and Science to the Washington DC area to meet with Army and NIH leaders, to tour a pilot bioproduction facility, and to coordinate plans with the consultant firm Price Waterhouse Coopers.

In addition to the efforts to advance and improve upon this successful RV144 regimen, the department is conducting laboratory analyses in support of other candidate vaccines including a subtype E (CRF01_AE) MVA vaccine candidate, and a DNA/MVA prime-boost candidate (RV262), and an AD26/MVA (RV307) prime boost regimen. RV262, entitled “Phase I Study of the Safety and Immunogenicity of PennVaxG DNA (Env (A, C, D) & consensus Gag) with IL-15 DNA Plasmid Adjuvant Administered by Intramuscular Biojector[®] 2000 Injection or by Intramuscular Electroporation using the CELLECTRA[®] Device Followed by MVA-CMDR (HIV-1 CM235 env/ CM240 gag/pol) Boost in Healthy, HIV Uninfected Adults” is completed in Rockville, MD for Part A and finished vaccination in August 2013 at all three East African sites (Kenya, Tanzania, and Uganda). The DSMB met to review interim safety data for the study on 30 January 2013 and deemed the study was well conducted and safe to proceed. The



Department provides immunomonitoring support for the study and the former department chief served as the protocol chair for this DAIDS-sponsored study. RV307 entitled “A Phase I Study of Prime-Boost Combinations Using Modified Vaccinia Ankara and Adenovirus Type 26 Vectors with Mosaic and Natural Inserts in Healthy, HIV-Uninfected Adults” was to be sponsored by Crucell Holland, BV and had been planned to start in May 2013 with the Royal Thai Army Clinical Research Clinic and the Department of Retrovirology serving as one of three clinical sites. The department orchestrated a great deal of study preparation in anticipation of commencement of this study. Unfortunately, delays in study start related to MVA product issues resulted in cancellation of the study. Division of AIDS money earmarked for this study will be reprogrammed to support future clinical vaccine development.

In support of vaccine development, the department initiated efforts to optimize methodologies for the collection and characterizations of mucosal secretions. Since HIV-1 penetrates immune defenses at mucosal surfaces, it is vital to understand immunological weaknesses exploited by the virus and improve conditions to prevent viral acquisition. In collaboration with TRC, RV335 tested new methodologies for the collection of vaginal and anal secretions. These new approaches improved the yield as well as the quality of samples collected. These methods have contributed significantly to scientific understanding of vaccine immune responses at mucosal surfaces in RV305, are being used in RV305, are planned for use in RV328, and future studies. In collaboration with Northwestern University, deconvolution microscopy capabilities for the characterization of antibody interactions with HIV-1 viruses in mucosal secretions in vaccine recipients was developed and optimized, and RV305 samples have been subjected to this technique, with final analysis pending.

Two clinically and immunologically intensive acute cohort studies (RV217 and RV254), to better characterize the virus-host interaction in the acute phase of HIV infection, with and without antiretroviral therapy continue to be successfully executed with progression to Phase B of the study and increased enrollment in 2013, respectively.

RV254, entitled “Establish and characterize an acute HIV infection cohort in a Thai high risk population” is a collaboration with the Southeast Asia Research Collaboration with Hawaii (SEARCH) and the Thai Red Cross AIDS Research Center (TRCARC). The study has successfully identified acutely HIV infected (Fiebig I/II) high-risk individuals from the Bangkok population through the Thai Red Cross Anonymous Clinic. As of the end of 2013, approximately, 150 acute infections confirmed and are enrolled in the protocol. After enrollment in the protocol, subjects are asked to consent to invasive procedures such as gut biopsies, lumbar punctures, leukapheresis, and to provide mucosal secretions such as semen and rectal fluid to characterize in detail the host-virus interaction in all immunologic compartments. Subjects are also offered early anti-retroviral therapy (ART) to evaluate the effects early treatment initiation on the course of HIV disease progression. The majority (98%) of volunteers elected to start ART and a large number (75%) agreed to undergo invasive procedures. Volunteers are mainly young MSMs and are infected with CRF01_AE, R5 tropic virus predominately identified in Fiebig 1 (50 subjects), Fiebig 2 (n = 25), and Fiebig 3 (n = 59). The protocol has been amended to increase enrollment to 500 and to include lymph node biopsies and data sharing is now established with the RV217 acute infection cohort in Pattaya. Results from this study are compared to HIV-negative individuals and chronically infected individuals enrolled under a separate protocol entitled RV304 “Characteristics of immune cells in gut mucosa of HIV negative and chronically HIV-infected Thais”. In 2014, at least three studies are planned to start that will enroll RV254 volunteers to receive experimental interventions including a monoclonal antibody or therapeutic vaccine that are hoped might cure some recipients of their HIV infection.

Search 013/RV304 is a service protocol intended to collect specimens in support of other protocols. This protocol allows the collection of peripheral blood, sigmoid biopsies, leukapheresis, and CSF collection. By the end of 2013, a cumulative total of 57 patients (37 HIV-



negative and 30 chronically HIV infected, treatment-naïve) volunteers have been enrolled in Search 013/RV304 to serve as comparators for patients recruited in the acute HIV-infection cohort Search 010/RV254. Furthermore this protocol is utilized to evaluate the usage of the IFN-gamma (IFN γ) ELISpot on mucosal mononuclear cells (MMC) isolated from sigmoid biopsies. The implementation of the IFN γ ELISpot will allow characterization of the HIV-specific mucosal immune responses for example in vaccinees using this stable, low cost and low cells-requiring assay.

RV217 is a multi-site cohort study (Thailand, Uganda, Tanzania, and Kenya) designed to identify and define high-risk behaviour, describe the 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. In Thailand, subjects are recruited from high-risk groups engaged in sex work in Pattaya. Subjects are enrolled, followed for two years with blood collection every 6 months after baseline studies and receive 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. As of February 2014, a total of 16,822 potential volunteers have been briefed and 847 volunteers have taken the ACASI questionnaire. The HIV prevalence amongst potential volunteers is 18.4%. Five hundred fifty-eight HIV negative volunteers have been successfully enrolled in the study. Forty incident cases have been detected with cumulative overall incidence in mid as of January 2014 of 4.81 per 100 person-years, ranging from 7.29 among men who have sex with men to 0.83 among female sex workers (who are no longer being recruited because incidence is too low to support study objectives. Approximately two thirds 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 78.5%.

The Department of Retrovirology Community Advisory Board (Retro CAB) was formed in July 2011. The CAB completed its membership, training, and was fully functional by July 2012. The Department, in conjunction with key NGOs and community engagement experts piloted the first UNAIDS-AVAC Good Participatory Practice guidelines training on biomedical HIV prevention trials for its CAB members, stakeholders, and CABs members from collaborating institutions. HIV research is unique in its history of community engagement and activism as well as the societal stigma associated with the infection. The department's community engagement team's mission is to maintain strong ties with the local community, potential subjects, and stakeholders in an effort ensure lines of communications are established and information regarding the clinical trials conducted by the department that impacts the community are relayed. The CAB remained active in 2013, continuing varied relevant training, and meeting 5 times to conduct capacity building training, and discuss protocols.

The department in 2013 stood up a non-human primate laboratory that will serve as a platform for basic science experiments that are not possible in humans. Multiple assays have been stood up in this laboratory, and planning for the first animal experiment that will include titration of a Simian-Human Immunodeficiency Virus in collaboration with MHRP and the Division of AIDS.

COLLABORATIONS

- NGOs and advocates
 - Foundation for AIDS Rights (FAR)
 - AIDS Access Foundation (ACCESS)
 - Thai Network of People Living with HIV/AIDS (TNP+ eastern)



- Thai NGO Coalition on AIDS (TNCA)
- Health and Opportunity Network (HON)
- Foundation for Service Workers In Group (SWING)
- MSM-Community Advisory Board (MCAB)
- The Poz Thailand
- Rainbow Sky Foundation
- Local and Regional
 - Royal Thai Army, Thai Ministry of Public Health,
 - Academic (Mahidol, Chulalongkorn, Chiang Mai),
 - Thai Red Cross, SEARCH (Southeast Asia Research Collaboration with Univ of Hawaii)
- USAID, Vietnamese Ministry of Defense (through PEPFAR support)
- U.S. Government
 - NIAID/DAIDS, NIAID/DCR/IDCRP
 - US PACOM/COE
 - USAID
 - US CDC
- International and Academic
 - WHO/UNAIDS
 - Global HIV/AIDS Vaccine Enterprise
 - HIV Vaccine Trial Network-Statistical Center for HIV/AIDS Research and Prevention (HVTN-SCHARP)
 - Duke University (Collaboration for AIDS Vaccine Discovery)
 - Sanofi Pasteur
 - Global Solutions for Infectious Disease (formerly VaxGen)
 - Novartis (formerly Chiron)
 - Gilead (ARV training grant)
 - Henry M Jackson Foundation
 - Crucell/Johnson and Johnson
 - EMMES
 - Northwestern University, Chicago, Illinois, USA.
 - New York University, New York City, New York, USA

FUTURE PLANS AND STRATEGIES

The immediate focus of the coming year is to complete the three follow on studies to evaluate and perhaps improve upon the immunogenicity of the RV144 regimen and to continue with the ongoing high-risk cohort protocols. New studies are being developed in both of these domains to focus on improving immunogenicity and to advance cure approaches, respectively. Evaluation and down-selection of HIV Env proteins and adjuvants for use in a phase 2B trial are being vigorously pursued and may include collaborations with the Gates Foundation, NIAID, Thai Ministry of Public Health, Thai Ministry of Science and Technology, U.S. Embassy, and Sanofi Pasteur, centered on AVEC-Thailand partnership