

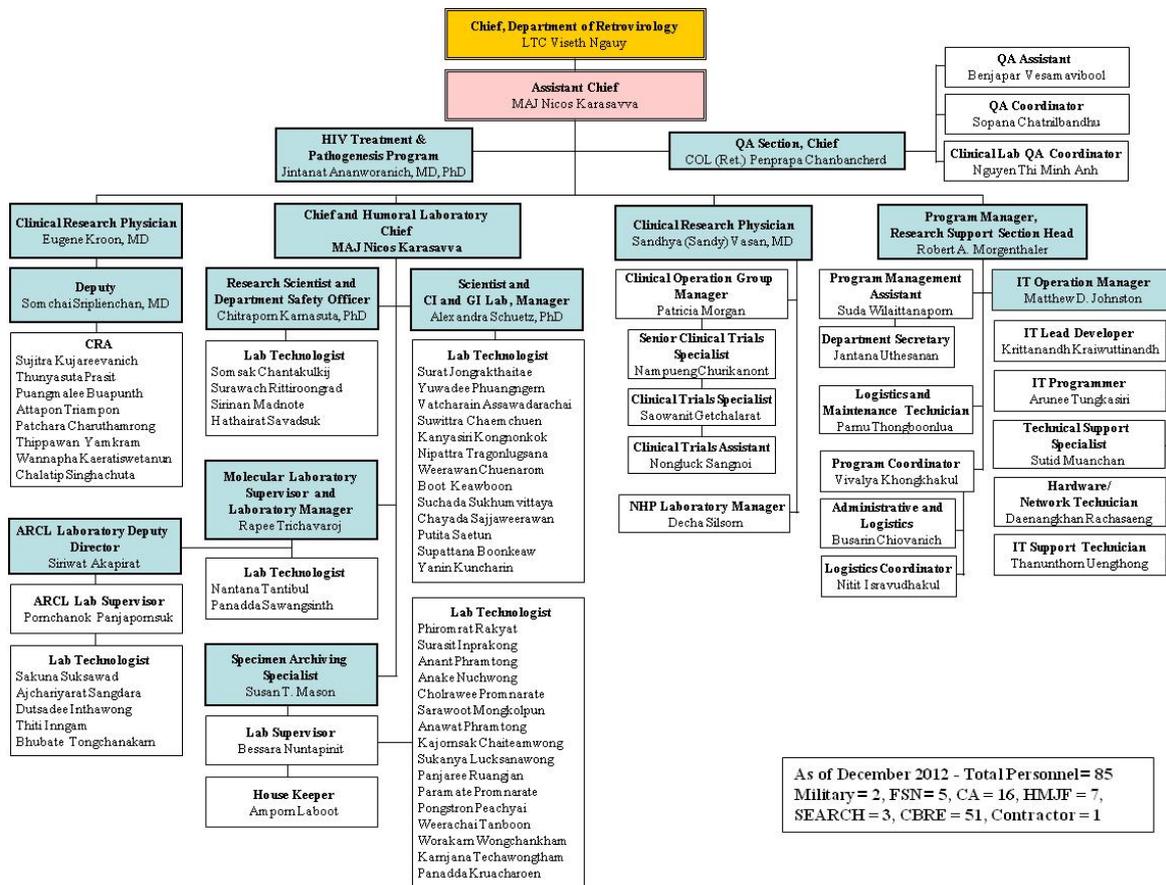
DEPARTMENT OF RETROVIROLOGY

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 81 staff that includes 2 Active-Duty Army Officers (1 Medical Corps, 1 Medical Service Corps). The department employs contracted employees and Thai nationals including 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 of Personnel 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
- Composite Risk Management
- Mandatory Ethics Training
- Computer User Training on “DoD Information Assurance Awareness Training”
- Mandatory EEO and Sexual Harassment Training

In-House Training of Personnel Provided by/or to the Department

- Quantifying Particle Diffusion Assay in Mucosal Secretion and Data Analysis Training to Mr. Somsak Chantakulkij and Mr. Surawach Rittiroongrat and, HI-TRC Laboratory, Bangkok, Thailand. August 2012 and December 2012, respectively
- Assist Other MHRP Laboratories with Implementing GCLP and Standard Operating Procedure (SOP) Development and Assistance for Maintaining CAP Accreditation or Equivalent
- Refresher GPP for RV217d staff, AFRIMS QAU, ECHO site Pattaya, Chonburi, Thailand, February 2012. Am I (and my institution) Qualified to Do Clinical Research? Dr. Eugene Kroon, Standard Course in Clinical Trials. Chulalongkorn University. 29 June 2012
- Basic GCP and GCP Refresher Training, PPD. AFRIMS. July 2012
- Advances in HIV Vaccine Development. Dr. Sandhya Vasani, U.S. Embassy and Thailand Ministry of Public Health Conference, Nonthaburi, Thailand. 10 October 2012
- Good Participatory Practice Guidelines for Biomedical HIV Prevention Training for Community Advisory Board of Vaccine Trial Center and VTC staff and RTA staff, AFRIMS, Bangkok, Thailand. November 2012

Outside Training of Personnel

- 15th Bangkok International Symposium on HIV Medicine, HIV-NAT. Bangkok, Thailand. January 2012
- Good Participatory Practice Guidelines for Biomedical HIV Prevention Training Workshop for RV217d Stakeholders. All Seasons Hotel, Pattaya, Chonburi, Thailand. February 2012
- CAVD/CA-VIMC Scientific Advisory Board and Full Group Meeting, Durham, N.C., U.S.A. 21-23 February 2012
- Good Participatory Practice Guidelines for Biomedical HIV Prevention Training for Community Advisory Board of Vaccine Trial Center and VTC staff, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. March 2012
- Annual Meeting of the Association of Medical Technologist of Thailand. Chiang Mai. April 2012

- HON Members Outing. Rattanakpura Resort, Chanthaburi, Thailand. May 2012
- CITI Program Training on “Biomedical Research Support Staff”, online, <http://citiprogram.org>. May 2011
- GCLP Training by Daniel A. Ozaki, Manager, CAVD/CA-VIMC Central Quality Assurance Unit. Duke Center for AIDS Research Central Quality Assurance Unit, Bangkok, Thailand. 16 May 2012
- 2nd PMK & AFRIMS Joint Symposium: Research Highlights on Infectious Diseases and Military Medicine. Phramongkutklao Hospital, Bangkok, Thailand. June 2011
- 2011 Quantifying Particles Diffusion Assay at Northwestern University. July 2012
- 11th HIV/AIDS Workshop 2012. Thailand Infectious Disease Association, Rajvithi Hospital, Bangkok, Thailand. 29-31 August 2012
- Training for Community Advisory Board’s Observers. Montien Hotel, Pattaya, Chonburi, Thailand. September 2012
- AIDS Vaccine 2012. Boston, M.A., U.S.A. 9-12 September 2012
- Clinical Pathology Network 2012. Phramongkutklao Hospital. November 2012
- Indonesia-Japan-Thailand (INiTha) Joint Forum on Infectious Diseases 2012. Institute of Tropical Disease, Airlangga University, Surabaya, Indonesia. December 2012
- Joint International Tropical Medicine Meeting 2011. Centara Grand & Bangkok Convention Center at Central World, Bangkok, Thailand. December 2011
- Visual Education for RV217d volunteer. Thai Nippon Rubber Industry, Chonburi, Thailand. December 2012

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 supported by 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 just two days after World AIDS Day on 3 December 2012 was graciously attended by U.S. Ambassador Kristie Kenney, RTA SG LTG Panuvich Pumhirun, AFRIMS leadership, representatives from the U.S. Military HIV Research Program and the Henry M. Jackson Foundation, and the staff of the Department of Retrovirology. The HVRC consolidates most 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. It is anticipated that all vaccinations will be completed in June 2013. An interim immunogenicity analysis will be conducted in March 2013 to assess if a late boost in prior vaccinees can augment the waning immune response. The results of this interim analysis will influence product development decisions.

Anticipated to start in the summer of 2013 are two additional advance development vaccine trials designed to address additional and alternative boosting strategies and to further elucidate which component of the vaccine regimen contributed to the success:

- 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"
- 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 addition to the efforts to advance and improve upon this successful RV144 regimen, new clinical trials are underway to test other candidate vaccines in the early stages of development, to include a subtype E (CRF01_AE) MVA vaccine candidate, 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 is expected to finish 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 Department Chief serves 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" is sponsored by Crucell Holland, BV and is expected 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. Both studies are in the techbased product development pathway and evaluate new candidate vaccines in the pipeline.

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 novel techniques have been implemented in all new clinical protocols and are shared with many collaborators. 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.

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 the upcoming FY13, 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 January 2013, approximately 58,908 samples have been screened, 104 acute infections confirmed and 86 volunteers 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 character 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 (28 subjects), Fiebig 2 (n = 10), and Fiebig 3 (n = 41). The protocol has been amended to increase enrollment to 150 and to include lymph node biopsies and data sharing is now established with another 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”.

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. In 2012, a total of 15 patients (10 HIV-negative and 5 chronically HIV infected, treatment-naïve) were 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 at the moment 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. A total of 1,362 potential volunteers have been briefed and 653



volunteers have taken the ACASI questionnaire. Six hundred and twenty one volunteers passed the screening visit and 467 HIV negative volunteers were successfully enrolled. Ninety two potential volunteers were HIV infected at baseline, for an overall prevalence of 14.1%. Thirty one incident cases have been detected with cumulative incidence in mid 2012 6.3% in TG, 5.85% in MSM and 0.94% in FSW. Some two thirds of the infected volunteers were captured during the very early stages of HIV infection (Fiebig stage I or II). Retention to the large blood draw visits and to finger stick small blood volume (twice weekly collections) has been approximately 75%. Another 150 subjects will be enrolled in Thailand, which incorporates vaginal and rectal swab collections and two questionnaires, a receptive risk questionnaire, and a genital cleansing questionnaire.

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 establish 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.

In 2012 the Retrovirology 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, we initiated protocol RV335 under which new methods were tested for the collection of vaginal and anal secretions. These new approaches improved the yield as well as the quality of samples collected. These novel techniques of mucosal collections have been implemented in all new clinical protocols and are shared with many collaborators. In collaboration with Northwestern University the department established deconvolution microscopy capabilities for the characterization of antibody interactions with HIV-1 viruses in mucosal secretions. This study is aimed at understanding antibody specificities induced by vaccinations and the improvement of vaccine design to generate more efficacious antibodies.

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)

Local and Regional

- Royal Thai Army, Thai Ministry of Public Health,
- Academic (Siriraj, Mahidol, Chulalongkorn, Chiang Mai),
- Thai Red Cross, SEARCH (Southeast Asia Research Collaboration with University of Hawaii)
- Thailand-U.S. CDC Collaboration
- USAID, Vietnamese Ministry of Defence (through PEPFAR support)

U.S. Government

- NIAID/DAIDS, NIAID/DCR/IDCRP
- U.S. PACOM/COE
- USAID
- U.S. CDC

International and Academic

- WHO/UNAIDS
- Global HIV/AIDS Vaccine Enterprise (GHAVE)
- Int'l AIDS Vaccine Initiative (IAVI)
- HIV Vaccine Trial Network-Statistical Center for HIV/AIDS Research and Prevention (HVTN-SCHARP)
 - Johns Hopkins Bloomberg School of Public Health
 - 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
 - GSK
 - Crucell/Johnson and Johnson
 - EMMES
 - Northwestern University, Chicago, Illinois, U.S.A.
 - New York University, New York City, New York, U.S.A.

SUMMARY OF 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. 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, NIAID, Thai Ministry of Public Health, Thai Ministry of Science and Technology, U.S. Embassy, and Sanofi Pasteur. Collaboration with the Department of Veterinary Medicine at AFRIMS for NHP work was initiated to support upcoming product development questions and to conduct novel basic science.

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 the conduct of cohort studies to identify high-risk populations in Chiang Mai, Bangkok and Pattaya for the next efficacy study.