

# The 2nd EMBLEM Update and Scientific Meeting

## Leveraging New Technologies to Answer Old Questions

22 – 26 September 2014

Kenya Medical Research Institute (KEMRI), Kisumu, Kenya.



EMBLEM scientists, staff, stakeholders and local government officials convened for the third time in four years to review accomplishments to date, to harmonize and standardize procedures across the sites, and to prepare to meet the goals of the coming year. These meetings provide opportunities to strengthen the team and the network of EMBLEM sites. The Kisumu meeting included, for the first time, presentations of BL findings by the Steering Committee, a training program focused on principal investigator responsibility training, and a meeting that established Afrilymph, a consortium to study BL across Africa.



### **Meeting Purpose**

The Second Epidemiology of Burkitt Lymphoma in East-African Children and Minors (EMBLEM) Update and Scientific Meeting was an opportunity for the study team from the Kenya, Tanzania, and Uganda to provide status updates; to once again share ongoing successes and challenges; to learn of the latest findings in Burkitt Lymphoma (BL) research from a number of scientific disciplines; and to obtain training in cancer research methods, and research project management. Attendees included clinical, administrative, and support staff from the EMBLEM sites; representatives of local government and other stakeholder institutions; international scientists; the project sponsor, National Cancer Institute (US); and staff from the African Field Epidemiology Network (AFENET) and Westat. In addition a concurrent Principal Investigator (PI) training session, sponsored by the Fogarty International Center of the National Cancer Institute was held on Wednesday morning and included PI Mentors from both NCI and the Centre for the Aids Programme of Research in South Africa (CAPRISA).

### **Venue**

The meeting was held at the conference facilities of the Kenya Medical Research Institute (KEMRI) at Kisumu, Kenya. The venue included one large conference room, which could be partitioned into two rooms to allow for the concurrent sessions on Wednesday morning. The EMBLEM Kenya team arranged for catered meals and coffee/tea breaks on the grounds, allowing additional opportunities for thought-provoking discussions and continued team interactions.

### **Attendees**

The meeting was attended by 105 persons, including EMBLEM staff, invited speakers, and guests. The combined audience consisted of research assistants, laboratory technicians, nurses, physicians, drivers, university professors, office managers, study monitors, project managers, pathology specialists, medical superintendents, data managers, study coordinators, and local government officials. The list of attendees is shown in Appendix 1. Certificates of attendance were distributed electronically following the meeting.

### **Overview**

The meeting included an opening session followed by sessions addressing BL Diagnosis, Pathology and Treatment; Epstein-Barr Virus (EBV), Malaria, and Helminths in BL; Genetic Factors in BL, Cancer Research Methods, a PI Workshop; Team Research Presentations; Research Project Management; Research Study Considerations; and a Closing Session. The meeting agenda is shown in Appendix 2.

## **Monday, September 22**

### ***Opening Session***

The opening session included welcome remarks from several EMBLEM and KEMRI officials, a poetry performance by local secondary school students, a song performed by Steven, the first successfully treated BL patient enrolled in EMBLEM Kenya, and several background presentations regarding BL and the EMBLEM study.

Dr. Peter Odada Sumba, EMBLEM co-PI from Kenya and KEMRI investigator, welcomed the assembled guests and expressed appreciation to the organizing committee and all those who assisted in coordinating the meeting. He served as a moderator for the session and introduced each speaker.

Dr. Stephen Munga, KEMRI director, extended his welcome to the meeting participants and gave a brief overview of KEMRI, including its role and mission to help map the way forward in medical research including BL and in advising the policy makers at the Ministry of Health.

Dr. Martin Ogwang, EMBLEM Co-PI and Medical Director of St. Mary's Lacor Hospital in Gulu, Uganda also extended his welcome, explaining that the history of EMBLEM staff meetings and the evolution to the goals of the current meeting -encouraging local leadership and capacity through ongoing training opportunities and also creating a sustainable research environment by strengthening existing systems and encouraging sharing and collaboration.

Dr. Lukoye Atwoli, Dean, Moi University School of Medicine delivered a presentation entitled "BL Research: Community Engagement," stressing the importance of involving the community at all stages of study design, implementation, and dissemination of results.

Eunice Juma and Rose Ochieng, students at Kobilu Mixed Secondary School performed a joint performance of a stirring poem about cancer written expressly for the meeting.

Dr. Kenneth Ofuso-Barko, Executive Director, AFENET extended greetings on behalf of AFENET and its affiliate training programs in Africa. He conveyed the AFENET vision of a healthier Africa and a hope of bringing a new order to bridge the political-technical divide.

Dr. Constance Tenge, EMBLEM Co-PI from Kenya welcomed the meeting participants on behalf of Prof. Sylvester Kimaiyo, Academic Model Providing Access to Healthcare (AMPATH) Chief of Party. Dr. Tenge explained that AMPATH works closely with Moi University, Moi Teaching and Referral Hospital (MTRH), and the Ministry of Health to foster the academic mission of care, education, and research. In addition, the AMPATH research laboratory provides services, personnel, processing, storage, and shipment of EMBLEM samples.

Dr. Sam Mbulaiteye, EMBLEM PI from NCI, provided an overview of the pathophysiology of BL, explaining that it is a rapidly growing but curable tumor, with co-factors of infectious origin – including EBV and malaria (*Plasmodium falciparum - Pf*).

Dr. Tobias Kinyera, EMBLEM study coordinator from Uganda, provided additional details about EMBLEM, the history of its implementation and community outreach, and a current

update of the study status at northwestern Ugandan sites of St. Mary's Lacor Hospital in Gulu and at Kuluva hospital in Arua. As of May 2014, EMBLEM Uganda had enrolled 288 cases, 613 matched population controls, 950 pilot population controls, and 184 health center controls.

Dr. Esther Kawira, EMBLEM Co-Investigator from Tanzania, provided a background of the BL experience and the current status of EMBLEM in Tanzania, with enrollment of 85 cases at the time of the meeting, with plans to deploy control enrollment during 2015.

Dr. Constance Tenge, EMBLEM co-Investigator from Kenya, provided an overview of BL in Kenya and EMBLEM implementation at HomaBay District Hospital in Nyanza Province and at Webuye District Hospital in Western Province. At the time of the meeting, EMBLEM Kenya had enrolled 165 cases with plans to begin control enrollment in 2015.

Dr. Sarah Awino, Physician at Moi Teaching and Referral Hospital (MTRH) welcomed the meeting attendees on behalf of Dr. Wilson Aruasa, MTRH Deputy Director of Clinical Services. She noted that benefits of the MTRH partnership with EMBLEM included staff training and leadership opportunities and the benefit to BL patients to treatment.

Dr. Francis Ogaro welcomed the meeting participants on behalf of Dr. John Kibosia, Chief Executive Officer of MTRH. He stressed the importance of establishing a system of obtaining drugs efficiently in order to reduce mortality in Kenya.

***Afternoon Session - Diagnosis, Pathology, and Treatment of BL***

This session highlighted the current approaches to BL treatment in each of the EMBLEM countries, an overview of the principles of BL treatment in Africa, additional welcome remarks, an overview of the EMBLEM approach to training African doctors in hematological procedures, and a panel discussion of the recommended direction of BL treatment in Africa.

Dr. Constance Tenge, EMBLEM Co-PI, Pediatrician, Moi Teaching and Referral Hospital, Eldoret; Dr. Esther Kawira, EMBLEM Co-PI; Director, Shirati Health Education and Development Foundation, Tanzania; and Dr. Valeria Calbi, EMBLEM Uganda, Hematologist, St. Mary's Lacor Hospital, Gulu, Uganda, provided an update on BL treatment in their respective countries.

Dr. Elizabeth Molyneux, Pediatrician/Researcher, Queen Elizabeth Central Hospital, Blantyre, Malawi reported on the Principles of Care in BL Treatment in Africa based on her experiences of treating children in Malawi.

Dr. Laurence Oteng, Homabay County Minister of Health, added his welcome remarks to the meeting attendees, noting the fortuitous combination of policy makers and health/medical researchers could accomplish more together to ensure the right to health.

Dr. Sam Mbulaiteye, EMBLEM PI from NCI delivered a presentation entitled "EMBLEM Experience Training Doctors in Hematological Procedures," referring to demonstration of best practices and study feasibility, building confidence, and managing costs with a primary focus on EMBLEM study procedures.

Panel Discussion: Drs. Elizabeth Molyneux, Constance Tenge, Valeria Calbi, Esther Kawira discussed “What We are Doing Well; What We Need to Do Better” and took questions and comments from the assembled attendees.

## **Tuesday, September 23**

### ***Morning Session - EBV, Malaria, and Rare Disease Considerations***

This session included an update on the role of micronutrients and malaria in BL in addition to design issues for studying rare diseases such as BL, and an assessment of key questions facing BL research in the near future.

Dr. Peter Odada Sumba discussed Micronutrient Deficiencies in BL. He described analyses showing that the interplay of multiple risk factors, including micronutrient deficiency and chronic malnutrition, may be necessary to set the stage for BL tumorigenesis in Africa.

Dr. Sam Mbulaiteye delivered a presentation entitled Malaria Phenotype Associated with BL. He reviewed the problem of identifying where malaria (*Plasmodium falciparum*, *Pf*) fits in the pathway of events leading to BL with evidence that studying malaria infection and antibodies are more informative than studying either alone and . Proof-of-concept studies of *Pf* arrays demonstrated the feasibility of studying many *Pf* proteins simultaneously in BL using protein arrays and that a restricted set of *Pf* peptides may be highly predictive of BL.

Dr. Fatma Shebl, Assistant Professor of Epidemiology at Yale University presented Study Design and Analysis Issues for Rare Diseases Such as BL. She discussed the definition, issues, and methods for studying rare diseases. These diseases do not affect more than 4 or 5 persons in 10,000 as defined by Japan and the European Union. Rare diseases such as BL are most commonly studied in case control studies and analyzed by calculating odds ratios.

Dr. Robert Tenge Kuremu, EMBLEM Co-PI, Moi University discussed the five key questions facing BL researchers as 1) why BL is more common among males, 2) has there been a change in the most common body site at presentation from jaw to abdomen and why, 3) what is the role of infectious agents such as malaria and EBV and which variants, 3) does genetic instability/polymorphism play a role, and 5) what is the role of environmental factors such as geographic location and climate?

### ***Afternoon Session - Genetic Factors in BL***

This session included a description of the Human, Heredity and Health Study in Africa; reports of the latest findings in EBV tumor genome, RNA sequencing, the B-cell receptor as oncogene, genetic risk factors of BL, and ethics of genetic research in Africa. In addition to genetic factors, this session also included an overview of malaria and BL in EMBLEM.

Samuel Kirimunda, EMBLEM Study Monitor, Biotechnologist, Infectious Diseases Institute, Kampala, Uganda, presented an overview of the Human, Heredity and Health Study in Africa. The goal of the effort is to develop a world-class biorepository of quality-assured biospecimens

available to both African and international researchers with the hope of enhancing genomic discoveries relating to Africa.

Dr. Kishor Bhatia, EMBLEM Co-PI, National Institutes of Health, USA presented EBV Tumor Genome in BL Cases from Different Geographical Regions. He reviewed several variation genome patterns and noted that EMBLEM presents the best opportunity for developing a comprehensive assessment of EBV genetic diversity and correlating EBV with disease to explore the role of EBV in cancer.

Professor Lorenzo Leoncini, Professor of Medical Biotechnology, University of Siena delivered a presentation entitled “Is BL a Poly-microbial Disease? Evidence from RNA Sequencing.” He reviewed results indicating that the frequency of mutations is much lower endemic BL than in sporadic BL and suggested that activation of B-cell receptor through an extrinsic antigen-driven signal could be present in endemic BL, positing a dependence on multiple pathogens.

Dr. Edus ‘Hootie’ Warren, Associate Professor, Department of Medicine, University of Washington, Fred Hutchinson Cancer Center, USA presented “The B Cell Receptor as Biomarker, Oncogene, and Therapeutic Target in Endemic BL.” The goal of his research is to harness the uniquely rearranged light and heavy chain genes of BL B cell receptors as both specific oncogenes and therapeutic targets.

Dr. Ludmila Prokunina-Olsson, Senior Investigator, National Institute of Health, NCI, USA – discussed Genetic Risk Factors of BL.

Professor Edwin Were, Moi University School of Medicine discussed ‘Ethics of Genomic Medical Research In Africa,’ noting protection of the participants as the main concern of multiple ethics committees in regional studies such as EMBLEM. Other challenges faced by EMBLEM include the involvement of children and the extensive poverty and illiteracy of the region.

Dr. Tobias Kinyera, Study Coordinator, EMBLEM Uganda reported on the “Malaria Profile in Endemic BL.” He cited ecologic and observational studies linking malaria infection and the frequency of endemic BL, but presented unadjusted findings from EMBLEM Uganda that BL cases were less likely to be positive for blood-stage malaria parasites, prompting the need for further analysis including additional causal factors.

## **Wednesday, September 24**

### ***Morning Session - Fogarty International Center (FIC)/Centre for the AIDS Programme of Research in South Africa (CAPRISA)***

**This jointly-sponsored workshop was designed to review the formal responsibilities of Principal Investigators and to provide interactive components allowing maturing scientists to learn about the opportunities, duties, and challenges of becoming a leader in medical research. The workshop was led by five successful African researchers from Kenya, Zimbabwe, Uganda and South Africa with experience in international collaboration. They provided participants with**

practical information about the multiple responsibilities of a PI in Africa, how to develop successful international collaborations in a competitive environment, and how to obtain research funding support for their ideas.

Dr. Kishor Bhatia, Director AIDS Malignancy Program, Office of HIV and AIDS Malignancy, NCI and Dr. Jeanne McDermott, Program Officer, FIC, NIH reviewed the purpose of the workshop and expressed an interest in building a bridge between intramurally funded programs like EMBLEM with extramurally funded programs as a way to develop successful African scientists.

Prof. Quarraisha Abdool Karim, Associate Scientific Director, CAPRISA (by video link from South Africa), provided a keynote address entitled “Pathway to an Independent Investigator,” highlighting the pathway of her career.

Dr. Jeanne McDermott presented an Introduction to the Role of a PI from the NIH Perspective. She provided the NIH definition and expectations of a PI in addition to sources of funding and tips regarding grant applications.

Prof. James Kiarie, Associate Professor of Obstetrics and Gynaecology at the University of Nairobi, moderated an interactive session entitled “What Should I do as a PI?” This session focused on challenges in research misconduct that a PI may face and included an interactive component regarding a possible study scenario involving non-dispensed drugs.

Dr. James Hakim, Professor of Medicine, University of Zimbabwe; and Moses Kamya, Professor of Medicine and Chair of the Department of Medicine, Makerere University College of Health Sciences and Mulago Hospital in Uganda; co-chaired an interactive session entitled “Opportunities and Challenges of International Collaborations.” Following descriptions of international collaboration from their own careers including their own interpretation of obstacles, solutions, and advancement prospects they faced, both mentors responded to questions from the attendees.

- Dr. Hakim listed access to a wide network of collaborators and researchers as an important opportunity in international collaboration, while organizational challenges such as limited resources could present significant challenges.
- Prof. Kamya listed access to additional resources as an important benefit of international relationships, but territoriality in project and data ownership are often substantial challenges to overcome when working with international partners.

Panel Discussion: Drs. Quarraisha Abdool Karim, Moses Kamya, James Kiarie, James Hakim and Thumbi Ndung'u, Investigator and Max Planck Institute for Infection Biology Research Group Leader at the KwaZulu-Natal Natal Research Institute for Tuberculosis and HIV (K-RITH) discussed “Golden Opportunities of a PI” and took questions and comments from the assembled mentees.

Dr. Sam Mbulaiteye delivered the workshop Wrap-up and Summary including a Follow-up Opportunity at CAPRISA. He summarized earlier presentations and announced that a follow-up

opportunity for more training would be awarded to applicants who would be selected for two weeks of practical training to develop a research concept idea into a grant proposal.

***Concurrent Morning Session followed by Afternoon Session: Research Methods Workshop***

This workshop was led by Dr. Fatma Shebl and included three lectures 1) Epidemiology and Study Design, 2) Measures of Association, and 3) Confounding, Mediation, and Interaction.

***Concurrent Afternoon Session – Consortium Planning Meeting***

Senior scientists gathered for this session to continue the discussion that began at the November 2013 AORTIC conference in Durban, South Africa

(<http://www.infectagentscancer.com/content/9/1/32>) regarding establishing a BL consortium.

Dr. Kishor Bhatia reviewed the potential benefits of establishing a consortium to pool samples and data to answer questions about this rare cancer and acknowledged the requirements establishing agreed upon policies for doing so. Dr. Sam Mbulaiteye provided an overview of consortium models for the study of rare cancers and explained that BL research in Africa is currently funded by single studies, but that a consortium would allow for greater funding independence, more comprehensive capacity building, and increased translation of findings to clinical practice. The consensus among the attendees was that forming a BL consortium would be a mutually beneficial endeavor. The participants proposed that the consortium should be called Afrilymph, and that Afrilymph could possibly begin with BL studies spun off from EMBLEM, but might in the future include studies of other lymphomas in Africa.

***Late Afternoon Session***

This session included team research presentations prepared by one team from each of the EMBLEM participating countries in response to a sample BIG CAT funding announcement from AORTIC to give the teams experience in preparing a research idea for funding. Each team presented a problem, specific aims, and study plan, and a budget. After presentation, each team received feedback from attending mentors.

Dr. Kristin Schroeder, Pediatric Oncologist, Duke University – currently working at Bugando Medical Center, EMBLEM Tanzania discussed the Tanzania team project “Barriers to Care: Downstaging through Social Media” to ultimately improve survival in BL patients.

Dr. Sarah Awino presented the Kenya team project, “Impact of Short Text Messages and Phone Calls on Spotting and Management of BL in East Africa,” also with a goal of improving survival.

Dr. Valeria Calbi, Hematologist, St. Mary’s Hospital, Lacor presented the Uganda team project “Implementation of a Burkitt Lymphoma Registry in East Africa” to promote additional research into the both etiology and management of BL.



## **Thursday, September 25**

### ***Morning and Afternoon Sessions - Research Project Management Workshop.***

These sessions focused on research project management from a variety of speakers affiliated with EMBLEM. Erisa Sunday, Senior Administrator, AFENET discussed budget management considerations followed by Dr. Kenneth Ofosu-Barko, AFENET Executive Director, who discussed using software as a way of tracking tasks and costs to manage stakeholder expectations. Drs. Kishor Bhatia and Dr. Steven Reynolds (EMBLEM Co-PI, National Institute of Allergy and Infectious Diseases - Uganda) discussed collaboration issues with international sponsors. Dr. Sam Mbulaiteye discussed the importance of team communication. Janet Lawler-Heavner, EMBLEM Study Manager at Westat, discussed EMBLEM project deliverables.

### ***Lessons Learned***

Following the project management presentations, the EMBLEM staff from each country met to develop a plan for implementing lessons learned from the research methods and project management sessions. An appointed representative from each team delivered a summary of lessons learned (Ismail Legason – Uganda, Dr. Kristin Schroeder – Tanzania, Titus Serem – Kenya).

## **Friday, September 26**

### ***Morning Session - Research Study Considerations***

This session included additional study considerations specific to EMBLEM. Andrea Towleron, the Warren Laboratory Manager at the Fred Hutchinson Cancer Research Center provided a detailed description of the samples collected for EMBLEM and what they are used for and what can be learned from them. Janet Lawler-Heavner led a brief discussion of proficiency testing in EMBLEM, including challenges of delivery, analysis, and possible solutions. Dr. Kishor Bhatia discussed data quality assurance, quality control, data receipt, and lag-time analyses. Dr. Moses Joloba, EMBLEM Study Monitor and Professor of Microbiology at Makerere University - Uganda, reviewed the role of the study monitors, emphasizing that the monitors play supporting rather than policing role – supporting the success of the study. Samuel Kirimunda, EMBLEM Study Monitor and biotechnologist at Infectious Diseases Institute, Kampala, Uganda, discussed corrective actions taken from EMBLEM site study monitoring, citing examples and noting the importance of identifying and eliminating the root cause.

### ***Closing Session***

Dr. Stephen Munga, KEMRI Director, once again addressed the gathering and expressed his appreciation for the depth of the presentations and the interest shown by those in attendance during the week. Dr. Sam Mbulaiteye also addressed the attendees, also remarking on the success of the meeting and the evidence of the increasing maturity of the research team and stakeholders involved, with praise for the outstanding leaders who provide collaboration and support. Dr. Constance Tenge again thanked the attendees for their attention and participation during the week-long meeting. She also thanked the conference organizers and support staff for the excellent coordination. Certificates of attendance will be forthcoming and will be distributed

electronically from Janet Lawler-Heavner at Westat. Finally, Dr. Martin Ogwang accepted the red planning flower as a symbol of his willingness to host the next meeting in Uganda in 2016.

***Meeting Accomplishments and Next Steps***

Throughout the meeting, EMBLEM staff, invited speakers, and various officials and stakeholders shared research and work experiences on the campus of KEMRI. The meals and coffee/tea breaks each day provided added opportunities for work and friendly conversations, enabling again the opportunity to build a strong team across many international boundaries. After the meeting closure by Dr. Constance Tenge, each EMBLEM country team had the opportunity to meet separately with Dr. Mbulaiteye to discuss next steps with respect to EMBLEM goals. The extended EMBLEM team looks eagerly forward to the September 2016 gathering in Uganda.