EBV conference establishes goals for defining
disease-related EBV subtypes for vaccine development

Laurie Goodman

The 2008 International Association for Research on Epstein-Barr virus and Associated Diseases (IARES) International Epstein-Barr Virus Genome Consortium (IEGC), Guangzhou, China; Goodman Writing & Editing, 14 Overbrook Terrace Natic, MA 01760 USA

Epstein-Barr virus (EBV), a γ-herpesvirus, was identified more than four decades ago. It is a ubiquitous infectious agent that infects more than 90% of the world’s adult population. Primary EBV infection in most individuals is asymptomatic or shows symptoms similar to other childhood illnesses. However, primary EBV infection in adolescents can cause infectious mononucleosis with symptoms that include sore throat, fever, and swollen glands. EBV infection can also affect the liver, heart, and spleen, but even in severe cases, it is rarely fatal.

Of greater concern, is that EBV infection has been closely linked with several malignancies, including ‘endemic’ Burkitt’s lymphoma, post-transplant lymphoma, acquired immune deficiency syndrome (AIDS)-associated lymphomas, Hodgkin’s disease, NK/T-cell lymphoma, gastric carcinoma, and nasopharyngeal carcinoma (NPC). In addition, there is evidence that EBV infection may underlie or be involved in the development of autoimmune disorders, including multiple sclerosis (MS), and chronic fatigue syndrome (CFS). Given EBV’s high infectious rate and the still limited understanding of its mechanisms for promoting such diseases, EBV is a serious world-health issue.

Researchers and public authorities involved in addressing widespread health crises met at the Thirteenth International Symposium on EBV and Associated Diseases (2008 EBV conference), held in Guangzhou, China. The purpose of the meeting was to discuss the impact of EBV on public health, to promote and stimulate an exchange of ideas, to communicate recent advances in research, and to advertise the availability of community materials for understanding and controlling this pandemic. The International Association for Research on Epstein-Barr Virus and Associated Diseases (IARES) hosted the conference, and Sun Yat-sen University served as the primary sponsor.

Yi-Xin Zeng (EBV Association President 2006-2008), the chair and director of Sun Yat-sen University Cancer Center and of the State Key Laboratory of Oncology in South China, welcomed the participants to the first EBV conference held in China, and to the city of Guangzhou, which is the frontier city for Xiao-Ping Deng’s opening and reforming policy. The meeting was held in the Guangzhou Baiyun International Convention Center, which is the largest, most modern convention venue in Southern China, and was named after one of the most famous landmarks in Guangzhou city, the Baiyun Mountain National Scenic Spot. Thus, in addition to stimulating scientific discourse, the attendees also enjoyed the inspiring scenery of a city whose natural beauty is often described by the words ‘pearl sea and white cloud’.

While the area is known for its beautiful setting, the meeting location was particularly suitable because Guangzhou is the capital of Guangdong province (also called Canton), where the incidence of NPC, an EBV-linked malignancy, is almost 100 times higher than that in Western countries. Thus, NPC is also called the Cantonese tumor. Highlighting this important issue was the specially-invited guest Professor Xian-An Zhang, director of the Basic Research Department of the Ministry of Science and Technology, who stated during the opening ceremony that holding the international EBV meeting in Guangzhou was extremely important as it is at the center of the NPC endemic area and is also the center for NPC research and treatment in China.

Professor Nancy Raab-Traub from Lineberger Comprehensive Cancer Center at the University of North Carolina, received the Henle Award at the conference, and gave an excellent overview of the history of progress in EBV research. The history of EBV work was perfectly balanced by the conference presentations that covered the latest advances in EBV biological research as well as its translational clinical applications. There were more than 270 participants from 13 countries, and 56 oral presentations, including six invited lectures, as well as 168 posters. The invited speakers discussed early events in primary B-cell infection, novel DNA repair inhibitory functions of Epstein-Barr virus nuclear antigen 1 (EBNA1), new cellular pathways that were targeted by EBV in pathogenesis of Hodgkin’s lymphoma, the role of EBV-encoded RNAs (EBERs) in the innate immunity system, and EBV genomic variation in NPC. Other significant advances in several
research areas included the identification of the functions of EBV-encoded miRNA, EBV-targeted novel imaging, and therapeutics.

Of great interest to the attendees, were the data showing the success of the human papillomavirus (HPV) vaccine in the prevention of cervical cancer. This stimulated a deep discussion for developing an EBV vaccine for the control of other EBV-related diseases. A round table meeting for EBV vaccine studies chaired by Professor Hans Wolf, from the Institute for Medical Microbiology and Hygiene at the University of Regensburg, brought together specialists whose research specifically focused on the development of preventive and therapeutic EBV vaccines. The presentation of convincing results achieved in the preliminary clinical trials of the EBV gp350 vaccine for controlling infectious mononucleosis were especially effective in promoting interest in and goals for developing broader useful vaccines.

Professor Yi Zeng from the Institute for Viral Disease Control and Prevention of the Chinese Center for Disease Control and Prevention in Beijing and his colleagues are working to control EBV-related malignancies using an EBV vaccine. This group is preparing to launch the first clinical trial of the latent membrane protein 2A (LMP2A) vaccine. This vaccine is specifically aimed at preventing NPC in Guangxi Zhuang Autonomous Region, China. However, some are still skeptical about the data supporting a link between EBV and NPC. Given such concerns, there is some debate as to whether there is enough basic research support to indicate the usefulness of launching this clinical trial. Given that evidence has shown only a few HPC subtypes can cause cervical cancer, the relationship of EBV subtype to disease remains uncertain. Thus, answering this question is critical for devising proper strategies to develop an effective EBV vaccine to control different EBV-related malignancies and diseases.

Many researchers believe that the highly concentrated region for NPC cases in Southern China does indicate that there is an EBV subtype in this area, and that it specifically promotes this type of cancer. Therefore, they feel that before useful vaccines can be developed, more research is required to demonstrate disease association with such an EBV subtype — not only for NPC but for other EBV-related diseases as well.

The importance for carrying out such a project had been raised in 1998 at the International NPC Meeting in Guangzhou. Due to the high cost and complexity of sequencing technology at that time, only one strain (GD1) from a Cantonese NPC patient was sequenced, with the results finally published in 2005. In addition to that strain, only one other (AG876) has been sequenced. However, the current widely available high-throughput, low-cost Next-Generation sequencing technology now makes this ambitious project possible.

With the advent of these new sequencing technologies, Yi-Xin Zeng appealed to the conference attendees to establish an International Epstein-Barr Virus Genome Consortium (IEGC) whose aim would be to determine if there are disease-associated EBV strains. The work would serve as a foundation to develop a disease-associated EBV strain vaccine(s). In principle, this would entail carrying out detailed genomic analyses of EBV strains from different regions as well as those derived from different EBV-related diseases. Several EBV research groups from around the world supported this proposal, and the agreement to do so was likely the most important achievement of the meeting. To carry out this project, Zeng suggested that they collect EBV-containing tissue samples of various diseases and from various areas, and then sequence the entire host-cellular and viral genomes from these samples. The newly formed consortium felt that at least 50 samples from each EBV-associated cancer would need to be analyzed in the study.

Sequencing for this large project is now well underway, and includes work on two NPC tumor tissue DNA samples from Guangdong area. For these, sequencing showed that EBV DNA was present along with normal genomic DNA, cancer-related mutated genomic DNA, and some microbial DNA. About 90% of the EBV genomic DNA could be reconstructed, and preliminary analysis indicated that the EBV genome contained a large number of variations or polymorphisms even between two samples from the two patients. Further analyses on these data as well as sequencing of other samples is ongoing and are expected to provide important information for best determining the means to control the spread of the virus and the impact of associated diseases.

Given the quality of the presentations at the meeting, and especially the establishment of collaborative large-scale goals among the community, such as the sequencing of multiple EBV subtype genomes, the conference deserved the opening ceremony promise from Professor Xian-An Zhang that research on EBV and EBV-associated diseases in Southern China would continue to receive strong support from the Chinese government. He believed that success of this conference would promote the progression of research on EBV and its related diseases in China and would enhance collaborations between Chinese scientists and their overseas colleagues.