Journal of Immunological Methods xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Immunological Methods

journal homepage: www.elsevier.com/locate/jim

Editorial

Introduction to a Special Issue of the Journal of Immunological Methods: Building Global Resource Programs to Support HIV/AIDS Clinical Trial Studies

Ana M. Sanchez [a,*], Thomas N. Denny [a], Maurice O'Gorman [b,c]

[a] Duke Human Vaccine Institute, Duke University Medical Center, Durham, NC, USA
[b] Departments of Pathology and Pediatrics, Keck School of Medicine, University of Southern California, USA
[c] Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 30 May 2014
Accepted 30 May 2014
Available online xxxx

Keywords:
EQAPOL
IQA
HVTN
IAVI
CHAVI
CAVD

ABSTRACT

This Special Issue of the Journal of Immunological Methods includes 16 manuscripts describing quality assurance activities related to virologic and immunologic monitoring of six global laboratory resource programs that support international HIV/AIDS clinical trial studies: Collaboration for AIDS Vaccine Discovery (CAVD); Center for HIV/AIDS Vaccine Immunology (CHAVI); External Quality Assurance Program Oversight Laboratory (EQAPOL); HIV Vaccine Trial Network (HVTN); International AIDS Vaccine Initiative (IAVI); and Immunology Quality Assessment (IQA). The reports from these programs address the many components required to develop comprehensive quality control activities and subsequent quality assurance programs for immune monitoring in global clinical trials including: all aspects of processing, storing, and quality assessment of PBMC preparations used ubiquitously in HIV clinical trials, the development and optimization of assays for CD8 HIV responses and HIV neutralization, a comprehensive global HIV virus repository, and reports on the development and execution of novel external proficiency testing programs for immunophenotyping, intracellular cytokine staining, ELISPOT and luminex based cytokine measurements. In addition, there are articles describing the implementation of Good Clinical Laboratory Practices (GCLP) in a large quality assurance laboratory, the development of statistical methods specific for external proficiency testing assessment, a discussion on the ability to set objective thresholds for measuring rare events by flow cytometry, and finally, a manuscript which addresses a framework for the structured reporting of T cell immune function based assays. It is anticipated that this series of manuscripts covering a wide range of quality assurance activities associated with the conduct of global clinical trials will provide a resource for individuals and programs involved in improving the harmonization, standardization, accuracy, and sensitivity of virologic and immunologic testing.

It has been more than 30 years since the emergence of HIV/AIDS and its subsequent progression to a pandemic. To date, the World Health Organization (WHO) estimates that almost 70 million people have been infected with HIV and about 35 million deaths have occurred from HIV infection or its complications.

Early in the pandemic, much attention was given to developing laboratory tests (e.g., antibody status) to determine if a person was infected. Later, focus turned to developing and validating tests to measure the level of viral activity (e.g., viral load) or to monitor the level of immune suppression (e.g., CD4 counts) induced as a result of HIV insult to the host. More recently, multi-site clinical study teams have been organized

* Corresponding author at: Dr. DUMC Box 103020 Durham, NC 27710, USA.
E-mail address: ana.sanchez@duke.edu (A.M. Sanchez).

http://dx.doi.org/10.1016/j.jim.2014.05.016
0022-1759/

to test novel antiretroviral regimens, early intervention, microbicides, host target cell genetic modifications, and HIV preventative vaccines across the globe. Increasingly, more complex laboratory assays have been developed in the hopes of finding markers of disease progression, response to therapy, or markers that may correlate with risk or protection from HIV infection after intervention.

In response to these efforts, global laboratory resource programs have supported the development of assay validation materials, standardized assay protocols, and external quality assessment programs for these assays in an effort to improve the harmonization, standardization, accuracy, and sensitivity of virologic and immunologic testing. These activities are broadly referred to as External Quality Assessment (EQA). An expected outcome of such EQA activities, including kit/assay development, training, monitoring via proficiency testing programs, and the corresponding remediation activities, is the development and maintenance of a network of high performing laboratories to support global clinical trials and endpoint analysis. EQA programs represent a critical component of the ongoing efforts to improve the sensitivity and reproducibility of immunological and virologic monitoring assays. Such efforts include the publication of guidelines for the performance of immune response assays (e.g., the Clinical and Standards Institute I/LA26-A2 guideline for performing single cell response assays) as well as recommendations for publishing studies that include immunological and virological testing procedures such as "Minimal information about a Flow Cytometry Experiment Standard (MiFlowCyt)" and "Minimal Information about T cell assays standards (MIATA)" (Lee et al., 2008; van der Burg et al., 2011; Britten et al., 2012). In this issue, Janetzki et al. provide an update on the current status on the adoption of the MIATA guidelines in the scientific literature and new tools available for easy implementation of the guidelines for authors and journals interested in adopting this new standard (Janetzki et al., 2014).

This Special Issue of the Journal of Immunological Methods summarizes quality assurance related activities of six global laboratory resource programs that support international HIV/AIDS clinical trials studies. The Immunology Quality Assessment (IQA) program monitors proficiency in immunophenotyping and PBMC cryopreservation. The External Quality Assurance Program Oversight Laboratory (EQAPOL) operates international proficiency testing programs for three functional immunological assays, as well as a Good Clinical Laboratory Practice (GCLP) production facility that has and continues to produce a repository composed of large panels of cultured virus representing the contemporaneous genetic diversity of HIV-1 globally. The HIV Vaccine Trial Network (HVTN) facilitates testing of preventative HIV vaccines through the conduct of clinical trials, from evaluating experimental vaccines for safety and immunogenicity, to testing vaccine efficacy. The Collaboration for AIDS Vaccine Discovery (CAVD) is a consortium of scientists dedicated to vaccine development and research. The International AIDS Vaccine Initiative (IAVI) supports vaccine research and development through research, advocacy, and partnership with academia, industry, and government organizations. The Center for HIV/AIDS Vaccine Immunology (CHAVI) was a consortium of universities and academic medical centers around the world working towards vaccine development and design. The CHAVI program operated from 2005 to 2012, and based on its success, two new CHAVI-Immunogen Discovery (CHAVI-ID) units were established to continue this important work. Each of these six programs have contributed publications to this issue of JIM including assay development, assay validation, proficiency material production activities, and proficiency program development.

1. EQA programs

The participation of global laboratories in EQA programs is critical for the execution of international clinical trials. A critical component of such EQA programs includes the external assessment of a laboratory's proficiency in all phases of testing from peripheral blood mononuclear cell (PBMC) isolation and cryopreservation to analytic (such as flow cytometry-based immunophenotyping) and to more complex functional immunological assays (such as detection of intracellular cytokines in specific leukocyte subsets or multiplex measurements of cytokines/chemokines and enzyme-linked immunosorbent spot [ELISpot] testing).

This issue provides an overview of the external quality assessment efforts of four global laboratory resources, EQAPOL, IQA Immunophenotyping program, CHAVI, and the HVTN. While not featured here, it should be noted that other HIV EQA programs, including the Virology Quality Assurance (VQA), IQA Cryopreservation Program and Clinical Quality Assurance Program (CQAP), have made contributions to EQA globally (Brambilla et al., 2001; Brambilla et al., 2004; Jennings et al., 2005; Weinberg et al., 2007; Jennings et al., 2012; DiFrancesco et al., 2013).

PBMCs are easily available from virtually any patient population of any age and represent the most frequently accessed patient material used for the assessment of vaccine- or therapy-induced immune functions. Given their critical importance, multiple programs have been developed to assess proficiency in PBMC isolation from peripheral blood, cryopreservation and storage (Misra et al., 1994; Weinberg et al., 2007; Olemukan et al., 2010; Aziz et al., 2013; Ducar et al., 2014; Sarzotti-Kelsoe et al., 2014b). This Special Issue highlights two programs' efforts to assess cryopreservation proficiency: HVTN and CHAVI. The paper by Ducar et al. describes the HTVN's development of automated, web-based tools, which enable the program to quickly collect, analyze, and report PBMC EQA data. Sarzotti-Kelsoe and Needham et al. implemented a program for the CHAVI studies to monitor PBMCs obtained from multiple international sites throughout the specimen-processing lifecycle: isolating, cryopreserving, handling, shipping, and storing at central repositories. Both EQA programs included many common elements to assess proficiency, including collection of processing quality indicators (e.g., processing time and viability), external quality control assessments, training of processing staff, implementation of network-approved SOPs for processing, and shipment of PBMCs to central repositories for further assessment and long-term storage. These programs have been able to identify non-conforming sites and were able to implement training and/or resources required to improve their performance, which led to their improvement over time.

The EQAPOL program currently administers three EQA programs: the interferon-γ T cell ELISpot assay (see (Sanchez et al., 2014b)), the Luminex based cytokine bead-based array assays (see (Lynch et al., 2014)), and the polychromatic flow cytometry-based intracellular cytokine staining (ICS) assays (Staats et al., 2014). Sanchez et al. provides a detailed

Please cite this article as: Sanchez, A.M., et al., Introduction to a Special Issue of the Journal of Immunological Methods: Building Global Resource Programs to Support HIV/AIDS Cli..., J. Immunol. Methods (2014), http://dx.doi.org/10.1016/j.jim.2014.05.016

description of the development of an external proficiency testing program designed to assess individual sites' performance of the interferon-γ T cell ELISpot assay. For this program, sites are provided with standardized peptides and cryopreserved PBMCs to run in their own in-house assays. In addition, they are provided with the reagents to run an ELISpot assay developed and standardized by EQAPOL, which is used to help troubleshoot what may be causing sub-optimal performance, if applicable. The program includes proficiency grading criteria for each of the following elements deemed essential in the execution of ELISPOT: timeliness, PBMC processing and handling, accuracy to the consensus, and precision.

Staats et al. describe the continuing development of an external proficiency program for ICS flow cytometry assays originally published in 2011 (Jaimes et al., 2011). The article describes the results of individual sites' performance and performance improvements through the comparison of local site-analyzed data versus data analyzed centrally at EQAPOL. Sites that perform poorly are offered remediation including discussions on protocol adherence, data analysis, and instrument performance. As the program develops from a 4 to an 8-color ICS assay platform, centralized analysis of FCS files for all sites will not be feasible and will require the development of automated analysis programs. The EQAPOL group is working towards the development and implementation of automated flow cytometry analysis tools reviewed by Richards et al. (2014). The team's goal is to have an automated analysis tool that can be used by both EQAPOL and each individual site in an effort to harmonize multiparametric flow cytometry data analysis (Richards et al., 2014).

The article by Lynch et al. discusses the development of an EQA program for Luminex-based cytokine bead array assays. The program was developed through collaborations with NIAID and the Cancer Immunotherapy Consortium (CIC) of the Cancer Research Institute. Through their efforts, a comprehensive external proficiency program was developed that includes a comprehensive send-out panel and the establishment of statistical grading criteria that allows for the relative comparison of each laboratory to a consensus. To our knowledge, this is the first and perhaps the only Luminex-based cytokines bead array proficiency program available, and thus this paper offers a unique perspective into how a proficiency program develops from the ground up.

A key element of any EQA program is a comprehensive grading system to assess site proficiency and to identify sites that need assistance. Rountree et al. discuss statistical methods employed to assess proficiency for the three different EQAPOL proficiency testing programs (Rountree et al., 2014). The EQAPOL Statistical group uses mixed effects models along with other statistical techniques to assess laboratory performance with respect to both precision and accuracy to the consensus. Mixed effects models allow for the incorporation of covariates, account for between and within site variability, and are useful for performing longitudinal analyses. They allow for a similar statistical methodological approach for the grading of each of the three proficiency testing programs, as well as allow for an analysis of trends over time.

The IQA Domestic CD4/CD8 program has been assessing site proficiency in clinical immunophenotyping for over 15 years. This longevity has provided a unique opportunity to analyze proficiency performance over time. The paper by Bainbridge et al. presents a statistical model-based method to analyze the performance of sites participating in this program over a ten-year period (Bainbridge et al., 2014). A model-based approach was selected because the donor samples are different for each send-out, each site uses their own methodology, and not all sites participated in the program during the entire analysis period. Using this approach, the group demonstrated that there was a significant reduction in inter-laboratory variability (i.e., improved precision) over time.

2. Support for network activities

Clinical trials are supported by multiple sites to enable access to the appropriate patient populations required for regulatory agency of the drug in coordination with technical resources needed for a trial. One of the benefits of multi-site laboratories is access to the resources needed to fully support the network's activities, such as Quality Assessment/Quality Control, proficiency testing, repository development, and assay development/validation. The paper by Todd et al. highlights the steps taken to implement GCLP guidelines within the EQAPOL program (Todd et al., 2013), which participates in all of these activities. As part of the process, the EQAPOL team developed standard operating procedures (SOPs) and quality management practices, implemented strict quality control procedures for equipment, reagents, and documentation, and received internal audits from the Quality Assurance oversight group. Operating under GCLP guidelines ensures all processes are well-planned, performed, and reported such that the entire process can be re-created. This is a key aspect of network assay performance for a program producing quality control reagents, maintaining a repository, and administering proficiency testing programs.

Garcia et al. and Sanchez et al. describe two repositories developed by global network laboratories, a PBMC repository and an HIV global virus panel. Garcia et al. describes a process by which PBMCs are isolated from leukopaks and cryopreserved to maintain both viability and functionality (Garcia et al., 2014). Cryopreserved PBMCs are used as Quality Control Materials (QCMs) to support proficiency testing programs operated by the CAVD, IQA, and EQAPOL. The methods described in this manuscript were employed to develop the PBMC repository described by Sambor et al. for the CAVD consortium (Sambor et al., 2014). The team demonstrated that the repository has maintained recovery, viability and functionality, including T, B and NK cellular functions. The repository is an invaluable resource for both the external proficiency programs and assay development. Cryopreserved and qualified PBMC in the repository are also made available to interested researchers.

Sanchez et al. describe ongoing efforts to build an HIV viral panel that represents the current geographical and genetic diversity of the virus (Sanchez et al., 2014a). Thus far, 100 viral samples have been cultured to achieve high-titers and high-volumes. Each sample is tested for sterility and well-characterized including near full-length sequencing, co-receptor usage analysis, viral load and p24 measurement. Similar to the PBMC repository, all EQAOPL Virus panel samples are available to approved researchers and commercial developers.

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Multi-site laboratories contribute to the immunological and virological testing by developing and validating new assays that support global vaccine trials. Sarzotti-Kelsoe et al. discuss the original optimization and validation of the TZM-bl assay for measuring antibody-mediated neutralization of HIV (Sarzotti-Kelsoe et al., 2013) in a manual and an automated platform, as part of the CAVD consortium. Similarly, Sarzotti-Kelsoe et al. (Sarzotti-Kelsoe et al., 2014a) detail the steps taken for the optimization and validation of the newer A3R5-based assay for neutralizing antibody measurement, which is reported to be more sensitive for detecting neutralization of tier two viruses (supported jointly by the EQAPOL and the CAVD consortia). The assay validation results including specificity, accuracy, precision, limits of detection and quantitation, linearity, range and robustness are presented.

The paper by Naarding et al. describes the development of a luciferase-based viral inhibition assay to evaluate vaccine-induced CD8 T cell responses (Naarding et al., 2013). This assay is more efficient, sensitive and cost-effective than previously developed viral inhibition assays, and will assist with selecting promising HIV-1 vaccine candidates capable of controlling HIV-1 replication.

3. Sustaining and expanding network activities

The work conducted by multi-site global laboratories involved in EQA activities such as proficiency testing, assay validation and repository development, require resources well beyond what any single laboratory would generally have. Support is needed to sustain and expand these critical network activities. In particular, there is a challenge with how best to meet the needs of sites requiring EQA services.

Currently, there are two main business models for EQA programs, one funded by the government or foundation support and another run by private industry as a fee-for-service. The EQA programs highlighted here are all funded by NIAID or foundation support. In this model, the EQA programs are offered to sites affiliated with the sponsor at no cost. In this model, independent laboratories (outside of the government or foundation affiliation) are not able to participate as the costs associated with administering the programs are born by another organization. As a way to expand participation in this business model, the EQAPOL program is currently exploring ways in which to offer independent laboratories a fee for service mechanism to participate in the proficiency testing programs. The other model requires site-associated costs commonly observed in commercial proficiency testing programs (e.g., College of American Pathologists). In this model, a participating site would pay an enrollment fee to be part of the proficiency testing program, and participation would be a requirement for ongoing accreditation. Any site can join one of these accreditation programs, provided they can pay the fee and meet the accreditation requirements.

Each of the teams providing articles in this issue have made important contributions to the HIV/AIDS global scientific community and helped advance our ability to develop new treatments or vaccine regimens. While more work is required to win the war against HIV/AIDS, the laboratories represented in this issue, which support discovery science or translational clinical trials, are well positioned for success going forward. We hope that this Special Issue of the Journal of Immunological Methods, highlighting their important contributions, will allow their intellectual reaches to expand well beyond their current participant sites.

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Please cite this article as: Sanchez, A.M., et al., Introduction to a Special Issue of the Journal of Immunological Methods: Building Global Resource Programs to Support HIV/AIDS Cli..., J. Immunol. Methods (2014), http://dx.doi.org/10.1016/j.jim.2014.05.016

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Please cite this article as: Sanchez, A.M., et al., Introduction to a Special Issue of the Journal of Immunological Methods: Building Global Resource Programs to Support HIV/AIDS Cli..., J. Immunol. Methods (2014), http://dx.doi.org/10.1016/j.jim.2014.05.016