Cancer Immunity (15 July 2013) Vol. 13, p. 13

Cancer Immunity Commentary

Structured reporting of T cell assay results

Sylvia Janetzki[1], Axel Hoos[2,3], Cornelis J.M. Melief[4], Kunle Odunsi[5], Pedro Romero[6] and Cedrik M. Britten[7]

[1]*ZellNet Consulting, Inc., Fort Lee, NJ, USA*

[2]*GlaxoSmithKline, Collegeville, PA, USA*

[3]*Cancer Immunotherapy Consortium of the Cancer Research Institute, New York, NY, USA*

[4]*Department for Immunhematology and Blood Transfusion, Leiden University Medical Centre, and ISA Pharmaceuticals, Leiden, The Netherlands*

[5]*Department of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY, USA*

[6]*Division of Clinical Onco-Immunology, Ludwig Center for Cancer Research, University Hospital (CHUV), Lausanne, Switzerland*

[7]*Translational Oncology at the University Medical Center of the Johannes Gutenberg-University Mainz gGmbH, Mainz, Germany*

Keywords: MIATA, T cell assay

Introduction

Recently, the final versions of the Minimal Information about T cell assays (MIATA) guidelines were published following a vetting process among peers. Here we summarize the rationale and background of the project and propose how to implement structured reporting of T cell experiments. Successful adoption by peers bears the potential, in the long-term, of enhancing the development of new immunomodulatory therapeutics.

Assays for the analysis of cell-mediated immunity belong to the essential repertoire of many laboratories involved in a variety of immunological sub-specialties, including oncology, infectious diseases, autoimmunity, transplantation immunology, and others. Flow cytometry-based as well as Elispot assays have been developed to investigate a wide range of analytes on a single-cell level and were refined for sensitive, reliable, and polyfunctional analysis. Over the years, the assay evolution occurring in institutions worldwide has led to optimized assays, but has left the scientific community with countless permutations of assay protocols and local standards. At the institutional level, the two main challenges are to define the biomarker assay which fits best to the investigational medicinal product in development, and to control the performance of applied analytical assays. From the community-wide perspective, the biggest challenge arises from the question of how to reliably interpret and compare results generated by different labs.

In this dynamic setting, the Cancer Immunotherapy Consortium of the Cancer Research Institute (CIC-CRI) and the Immunoguiding Program of the Association for Cancer Immunotherapy (CIP-CIMT) initiated proficiency panel programs for the most commonly used T cell assays involving a large number of heterogeneous labs from different backgrounds (1). These panels revealed that results from testing the same samples can vary significantly between labs (2, 3). Hence, the heterogeneous landscape of T cell immune assays not only is reflected by the use of different protocols, but also directly translates into wide-spread variability in assay results. Data obtained from these large-scale proficiency panels enabled the identification of critical variables in assay design and conduct that can influence assay results (Figure 1).

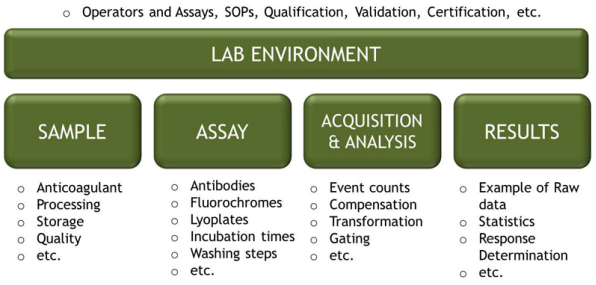
Crucial findings from these efforts were summarized in harmonization guidelines for the community (3-6). In subsequent panels, the implementation and adherence to such harmonization guidelines were successful in improving the accuracy of assay results overall and reducing the variability among labs (7). However, it was noted early on that most publications on T cell-related immune monitoring data lack structured reporting of all the critical protocol variables that may influence assay results, which may prevent easy interpretation of reports and limit comparability of data generated across institutions.

To address this issue, the Minimal Information About T Cell Assays (MIATA) project was initiated to define reporting guidelines, mirroring similar Minimal Information (MI) projects that were initially developed for high-throughput genomic assays and successfully applied for a variety of other assays (2, 8, 9). Importantly, MIATA was started and carried out as a broad effort to reach consensus on the minimal information necessary to efficiently and transparently describe how T cell assays were performed such that peers can confidently understand and interpret the presented data. While this was the project's driving force, another question of similar significance to be asked was: what and how much are scientists willing to share? Consequently, the MIATA project included an intense vetting process with two public consultation periods and two open workshops, with constant outreach to the community, over the time frame of three years (10). A dedicated website (11) was created that comprehensively displays every step, comment, and participant contributing to the project. With the input of more than 120 peers from academia and industry, as well as from regulatory background, the MIATA guidelines were recently finalized (12). The guidelines are divided into five modules and additional sub-modules which relate to the information concerning the sample, the specific assay protocol, the data acquisition, and analysis, as well as the lab environment—all process parameters identified earlier to be critical variables that can influence assay results. The guidelines are also visible on the MIATA website.

How to implement MIATA at an institution

Clearly, the mere existence of guidelines will not automatically lead to more structured reporting of experimental procedures

Figure 1



Examples for sources of variation for cellular assays. All of these variables have been shown to impact assay performance.

and results. Thus, the focus is now on implementation. To assist investigators and to demonstrate the straightforward nature of MIATA implementation, various supporting documents are provided online for guidance during the initial implementation phase. Here, the key information is displayed in a digestible format and includes (i) a checklist of the assay information required for MIATA compliance, (ii) examples of reports for ICS, Elispot, and multimer staining that follow the MIATA reporting framework, (iii) guidance for donor information, and (iv) definition of terms related to the laboratory environment. In addition, various publications already exist that fulfill the requirements for MIATA (6, 9, 13-15). Even with this available resource, it will certainly take more or less effort of authors to adapt the Materials and Methods section to the MIATA framework. Some publications already exist with detailed reporting on T cell assays, and here little, if anything, has to be added. In such cases, authors may consult the MIATA website to verify that the publication meets all MIATA criteria (16).

For authors who previously published abbreviated versions of their assays description, it can be useful to follow the module flow of the actual guidelines and report accordingly. Reporting on large studies which employed multiple T cell assays might require the use of the supplemental section of papers. Once an investigator spends the effort to structure a report accordingly, it will be much easier to compose follow-up reports. It may also be considered to establish a MIATA-compliant Materials and Methods section once, and later refer to this specific publication as long as the same protocol was employed, and only update new manuscripts with original study-specific information (e.g., sample information).

Implementation of MIATA in the field

The key for success of MIATA will lie in its broad adoption and regular use by the scientific community at large. The implementation process will need to involve two major players: the scientists reporting on T cell data and the journals including editorial teams and reviewers. The authors of this commentary envision a bottom-up activity from the T cell aficionados, rather than a top-down approach in which journals enforce adherence as a mandatory measure.

Incentives that encourage authors to follow MIATA guidelines may help support such a bottom-up approach. First, acknowledgement of MIATA compliance by journals may provide important validation for authors who have chosen to report their assay information in accordance with the MIATA framework. Second, by listing adherent manuscripts on the MIATA homepage, the MIATA designation may serve to increase awareness and alert more readers to such publications, leading to increased numbers of downloads in the short-term and possibly more citations in the long-run. The latter will benefit authors and publishers alike.

For the realization of these incentives, journals will need to allow explicit and visible use of the acknowledgement for those publications that fulfill the MIATA criteria. Offering the choice of using MIATA without enforcing it should be the way to proceed.

Certainly, the question arises about who verifies manuscripts for compliance with MIATA guidelines. A detailed answer could be at the discretion of the respective journals. A simple answer could be that authors may indicate within their manuscript if they adhere to MIATA (passive label assignment). Alternatively, dedicated reviewers may confirm adherence and assign the label actively. Once a manuscript is accepted and has been reviewed and confirmed to be MIATA-adherent, the author(s) or the journal can notify the MIATA core team, which will list the published paper online and include a link to the actual paper/journal.

As mentioned earlier, the journals, including editorial teams and reviewers, will be an integral part of the successful adoption of MIATA by authors and, in turn, among the community at large. The provision of an optional choice, such as within the instructions for authors or editorial policies, to report in accordance with the MIATA framework, could support the adoption rate.

A similar process already took place for the reporting on microarray data, which started with the free choice adoption of the MIAME guidelines (14) and led to the integration of MIAME in authors' instructions by some journals who have adopted it. In other words, microarray data cannot be published in these journals without MIAME compliance, a result achieved from bottom up, but not forced down upon the community.

Discussion

While much effort within the community is needed to successfully implement MIATA, recent developments allow an optimistic view. An increasing knowledge exists about MIATA. The initial MIATA announcement has been cited more than 80 times, and the first adherent papers have been published (9). Many important stakeholders in different fields of immunology were and are enthusiastically involved in the project, and large organizations in Europe and the USA support the project's goal. This is largely because MIATA is part of bigger and complex efforts to provide tools to the community that can improve T cell assays and to guide the development of new immunotherapies (17). These efforts further include structured proficiency panel programs, assay harmonization, standardized response determination methods, availability of reference samples, automation of analysis procedures, and more. In the case of immuno-oncology, MIATA integrates well into a paradigm that encompasses peculiar features of immunotherapies that target the immune system and other, classical therapies that target the tumor (18).

Abbreviations

MIATA, Minimal Information About T Cell Assays

References

1. Britten CM, Janetzki S, van der Burg SH, Gouttefangeas C, Hoos A. Toward the harmonization of immune monitoring in clinical trials: quo vadis? *Cancer Immunol Immunother* 2008; **57:** 285-288. (PMID: 17721782)

2. Janetzki S, Britten CM, Kalos M, Levitsky HI, Maecker HT, Melief CJM, Old LJ, Romero P, Hoos A, Davis MM. "MIATA"-minimal information about T cell assays. *Immunity* 2009; **31:** 527-528. (PMID: 19833080)

3. Janetzki S, Panageas KS, Ben-Porat L, Boyer J, Britten CM, Clay TM, Kalos M, Maecker HT, Romero P, Yuan J, Kast WM, Hoos A, Elispot Proficiency Panel of the CVC Immune Assay Working Group. Results and harmonization guidelines from two large-scale international Elispot proficiency panels conducted by the Cancer Vaccine Consortium (CVC/SVI). *Cancer Immunol Immunother* 2008; **57:** 303-315. (PMID: 17721781)

4. Britten CM, Gouttefangeas C, Welters MJ, Pawelec G, Koch S, Ottensmeier C, Mander A, Walter S, Paschen A, Müller-Berghaus J, Haas I, Mackensen A, Køllgaard T, thor Straten P, Schmitt M, Giannopoulos K, Maier R, Veelken H, Bertinetti C, Konur A, Huber C, Stevanovic S, Wölfel T, van der Burg SH. The CIMT-monitoring panel: a two-step approach to harmonize the enumeration of antigen-specific CD8+ T lymphocytes by structural and functional assays. *Cancer Immunol Immunother* 2008; **57:** 289-302. (PMID: 17721783)

5. Britten CM, Janetzki S, Ben-Porat L, Clay TM, Kalos M, Maecker H, Odunsi K, Pride M, Old L, Hoos A, Romero P, HLA-peptide Multimer Proficiency Panel of the CVC-CRI Immune Assay Working Group. Harmonization guidelines for HLA-peptide multimer assays derived from results of a large scale international proficiency panel of the Cancer Vaccine Consortium. *Cancer Immunol Immunother* 2009; **58:** 1701-1713. (PMID: 19259668)

6. Attig S, Price L, Janetzki S, Kalos M, Pride M, McNeil L, Clay T, Yuan J, Odunsi K, Hoos A, Romero P, Britten CM, CRI-CIC Assay Working Group. A critical assessment for the value of markers to gate-out undesired events in HLA-peptide multimer staining protocols. *J Transl Med* 2011; **9:** 108. (PMID: 21745365)

7. Janetzki S, Britten CM. The impact of harmonization on ELISPOT assay performance. *Methods Mol Biol* 2012; **792:** 25-36. (PMID: 21956498)

8. Taylor CF, Field D, Sansone S-A, Aerts J, Apweiler R, Ashburner M, Ball CA, Binz PA, Bogue M, Booth T, Brazma A, Brinkman RR, Michael Clark A, Deutsch EW, Fiehn O, Fostel J, Ghazal P, Gibson F, Gray T, Grimes G, Hancock JM, Hardy NW, Hermjakob H, Julian RK Jr, Kane M, Kettner C, Kinsinger C, Kolker E, Kuiper M, Le Novère N, Leebens-Mack J, Lewis SE, Lord P, Mallon AM, Marthandan N, Masuya H, McNally R, Mehrle A, Morrison N, Orchard S, Quackenbush J, Reecy JM, Robertson DG, Rocca-Serra P, Rodriguez H, Rosenfelder H, Santoyo-Lopez J, Scheuermann RH, Schober D, Smith B, Snape J, Stoeckert CJ Jr, Tipton K, Sterk P, Untergasser A, Vandesompele J, Wiemann S. Promoting coherent minimum reporting guidelines for biological and biomedical investigations: the MIBBI project. *Nat Biotechnol* 2008; **26:** 889-896. (PMID: 18688244)

9. *MIATA compliant publications.* Accessed from: http://miataproject.org/index.php?option=com_content&view=article&id=133&Itemid=28

10. Britten CM, Janetzki S, Van der Burg SH, Huber C, Kalos M, Levitsky HI, Maecker HT, Melief CJ, O'Donnell-Tormey J, Odunsi K, Old LJ, Pawelec G, Roep BO, Romero P, Hoos A, Davis MM. Minimal information about T cell assays (MIATA): the process of reaching the community of T cell immunologists in cancer and beyond. *Cancer Immunol Immunother* 2011; **60:** 15-22. (PMID: 21080166)

11. *The MIATA Project.* Accessed from: http://miataproject.org/

12. Britten CM, Janetzki S, Butterfield LH, Ferrari G, Gouttefangeas C, Huber C, Kalos M, Levitsky HI, Maecker HT, Melief CJ, O'Donnell-Tormey J, Odunsi K, Old LJ, Ottenhoff TH, Ottensmeier C, Pawelec G, Roederer M, Roep BO, Romero P, van der Burg SH, Walter S, Hoos A, Davis MM. T cell assays and MIATA: the essential minimum for maximum impact. *Immunity* 2012; **37:** 1-2. (PMID: 22840835)

13. Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A, June CH. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. *Sci Transl Med* 2011; **3:** 95ra73. (PMID: 21832238)

14. Singh SK, Meyering M, Ramwadhdoebe TH, Stynenbosch LF, Redeker A, Kuppen PJ, Melief CJ, Welters MJ, van der Burg SH. The simultaneous *ex vivo* detection of low-frequency antigen-specific CD4+ and CD8+ T-cell responses using overlapping peptide pools. *Cancer Immunol Immunother* 2012; **61:** 1953-1963. (PMID: 22491788)

15. Chudley L, McCann K, Mander A, Tjelle T, Campos-Perez J, Godeseth R, Creak A, Dobbyn J, Johnson B, Bass P, Heath C, Kerr P, Mathiesen I, Dearnaley D, Stevenson F, Ottensmeier C. DNA fusion-gene vaccination in patients with prostate cancer induces high-frequency CD8(+) T-cell responses and increases PSA doubling time. *Cancer Immunol Immunother* 2012; **61:** 2161-2170. (PMID: 22729556)

16. *MIATA checklist.* Accessed from: http://www.miataproject.org/checklist.pdf

17. van der Burg SH, Kalos M, Gouttefangeas C, Janetzki S, Ottensmeier C, Welters MJ, Romero P, Britten CM, Hoos A. Harmonization of immune biomarker assays for clinical studies. *Sci Transl Med* 2011; **3:** 108ps44. (PMID: 22072636)

18. Hoos A, Britten CM, Huber C, O'Donnell-Tormey J. A methodological framework to enhance the clinical success of cancer immunotherapy. *Nat Biotechnol* 2011; **29:** 867-870. (PMID: 21997622)

Contact

Address correspondence to:

Sylvia Janetzki, M.D.
Zellnet Consulting, Inc.
555 North Avenue, Suite 25-S
Fort Lee, NJ 07024
USA
Tel.: + 1 201 346 0710
Fax: + 1 201 346 0715
E-mail: sylvia@zellnet.com