Profiling of T cell Responses in Recent African Immigrants Identifies a Cluster of Antigens Associated with Clinical Malaria Episodes.

LeeAnn Talarico1, Zheng Yan1, Aula Alami1, Noelle B. Patterson1,2, Emily C. Smith1,3, Joao Aguia4,5, Martha Sedegah2, Thomas L. Richie2, Eileen F. Villasante3, Tobias Guenneb, Scott Marshall1, Jessica Baker Flechtner1 and Jean-Luc Bodmer1.

1Genocia Biosciences, Inc. Cambridge MA, USA. 2Naval Medical Research Center, Silver Spring MD, USA. 3Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda MD, USA. 4Camris International, Bethesda MD, USA. 5Biolat Solutions, Inc. Frederick MD, USA

Abstract

Memory T cell responses induced as a result of Plasmodium falciparum (P) exposure are difficult to measure, and a paucity of information exists on the correlation between responses to specific antigens and clinical outcomes due to exposure. We hypothesized that profiling T cell responses from donors who are recent immigrants to malaria-endemic areas, and correlating the antigen specificity of responses with reported episodes of clinical malaria, could help in identifying biomarkers of protection or disease. To develop and optimize a T cell antigen discovery platform, ATLAS™, based on expressed proteomic libraries of medically relevant pathogens. With this technology, the full or partial proteome of a pathogen is expressed as individual clones in E. coli, which can be processed by any donor’s antigen presenting cells and presented as peptide epitopes in the context of MHC class I or II molecules. When autologous CD8+ or CD4+ T cells are added that are specific for the clone in a given well, a functional readout of activation can be measured such as IFNγ. We constructed an expression library containing 735 full length Plasmodium falciparum 3D7 proteins predicted to be expressed during the liver stage of the parasite in endemic areas. This library was used to interrogate memory CD8+ T cell responses from a cohort of ~100 donors who had recently (18 months or less) emigrated from sub-Saharan Africa to the United States. Multivariate clustering of the screening data revealed a discrete set of 15 antigens that were correlated 14:1 to a prior clinical episode of malaria when compared to those with no prior clinical malaria episode. In summary, the ATLAS™ technology identified the antigen specificities of memory T cell responses that were generated during natural P exposure, a subset of which correlated to a history of clinical disease. We have identified biomarkers of clinical malaria exposure and work is ongoing to determine if these antigens are also recognized by T cells of protected vaccinated individuals.

Study Design

This study was designed to use the ATLAS™ platform to interrogate CD8+ T cell memory responses to individual recombinantly expressed full-length Plasmodium falciparum 3D7 antigens. Donors were composed of recent immigrants to the United States from sub-Saharan Africa. Blood was collected by African Services Committee in Harlem, NY and donors were assigned to 1 of 5 cohorts based upon their responses to a questionnaire.

Conclusions

• An expression library containing 735 full-length P. falciparum 3D7 proteins predicted to be expressed during the liver-stage of the parasite was constructed to interrogate CD8+ T cell memory in donors from malaria-endemic areas.

• Whole blood samples were collected from four distinct cohorts of volunteers upon their immigration into the United States at the African Services Committee in Harlem, NY. These cohorts represent different patterns of natural exposure to Plasmodium falciparum in endemic areas.

• The ATLAS™ technology platform was used to screen the donors’ CD8+ T cells against each individual full length protein in the library and identified multiple protein targets of recall T cell responses.

• Clustering analysis revealed 15 antigens, T cell responses to which predicted clinical malaria exposure.

• Experiments are currently underway to confirm malaria exposure by Indirect Fluorescent Antibody (IFA) testing at the NMRC.

• Additional analysis to identify antigens that segregate with protection from clinical malaria is ongoing.

Table 1: Cohort Definition and Recruitment.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Definition</th>
<th>Endemic</th>
<th>Prophylactic</th>
<th>Naive</th>
<th>Return</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td>Donors who have never traveled outside of the United States</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Endemic 1</td>
<td>Donors who have lived in a malaria endemic area for 18yrs or greater and have never had a previous exposure to malaria</td>
<td>40</td>
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<td>20</td>
</tr>
<tr>
<td>Endemic 2</td>
<td>Donors who have never traveled outside of the United States and have a negative history of malaria</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
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