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Antigen discovery for the identification of vaccine candidates and biomarkers using a T cell driven approach in combination with positional scanning peptide libraries

Valeria A. Judkowski[a], Radleigh G. Santos[b], Gonzalo Acevedo[c], Marc A. Giulianotti[b], Jon R. Appel[a], Silvia Longhi[c], Karina A. Gomez[c] and Clemencia Pinilla[a]

[a]*Torrey Pines Institute for Molecular Studies, San Diego, CA 92121, USA*
[b]*Torrey Pines Institute for Molecular Studies, Port St. Lucie, FL 34987, USA*
[c]*Instituto de Investigaciones en Ingenieria Genetica y Biologia Molecular, Buenos Aires, Argentina*

Abstract

The prevention and treatment of infectious diseases is highly dependent on the availability of reliable diagnostic tests and protective or therapeutic vaccines. There also exists an urgent need to develop reliable biomarkers to monitor treatment success and to predict disease progression from asymptomatic to symptomatic disease in several disease scenarios. The elucidation of the disease-relevant antigens that elicit the protective immune responses is critical and required for the development of biomarkers, diagnostics, and vaccines. However; one of the main obstacles to the study of antigen specificity in human T cells is their low frequency in PBMC samples. To overcome this problem we have implemented strategies to generate memory T cell libraries and clones specific to the pathogen of interest. Due to the fact that memory T cells represent a repository of the human T cell response to infection, examination of their antigen specificity can efficiently reveal immunogenic and relevant antigens involved in the *in vivo* response to infection or vaccines. To examine the specificity of the memory T cells we use an unbiased collection of antigens together with an *in silico* analysis, namely positional scanning based biometrical analysis. Here we present a summary of our approach and ongoing work on the development of strategies for the culture of memory T cells from patients with Chagas disease. While most studies focus on the identification of vaccine candidates using preselected immunogenic proteins derived from animal models or by or bioinformatics prediction, here we present an innovative approach that directly examines the specificity of the memory response following infection or immunization in humans.

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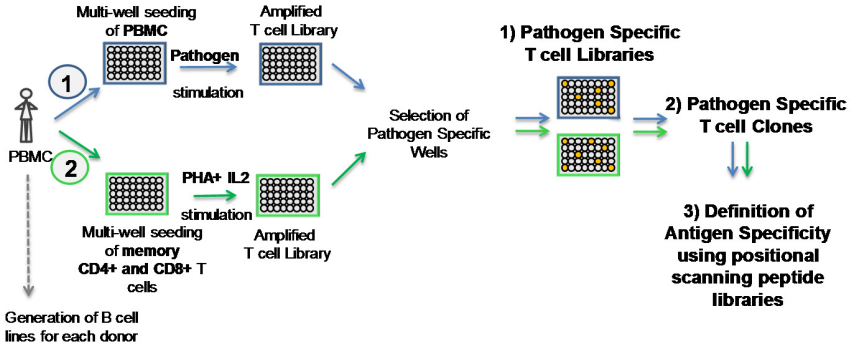
1. Introduction

To date, several studies aimed to identify T cell vaccine candidates have used preselected immunogenic proteins derived from experimental analysis on animal models or by bioinformatics prediction of MHC binding. While it is feasible to obtain candidate genes or proteins from bioinformatics analysis, their validation as immunogens is critical and more difficult, requiring further characterization of their immune recognition in humans. Here we describe the advantages and future required optimization steps to a "T cell driven" approach developed by our laboratory that uses human peripheral blood mononuclear cells (PBMC) from vaccinated or infected human patients to generate pathogen specific memory T cell libraries and clones to directly examine their specificity using an unbiased collection of peptides named positional scanning peptide libraries.

2. Results

The approach presented here consists of 3 steps: 1) the generation of T cell libraries representing the human memory response to infection or vaccination, 2) the generation of pathogen specific T cell clones and, 3) the screening of the pathogen specific T cell clones with positional scanning peptide libraries to identify *pathogen* immunogenic proteins (Figure 1).

Figure 1. T cell driven approach.



The 3 steps of the approach have been validated by our work and the work of others. Specifically, the generation of T cell libraries has been successfully used by Lanzavecchia's group to study the immune response to naturally processed parasite antigens from tetanus toxoid, cytomegalovirus and purified protein derivative[1] and more complex pathogens such as *S. pyogenes, S. aureus and C. albicans*[2,3]. In addition, work from our laboratory in collaboration with the Chagas Laboratory at Instituto de Investigaciones en Ingeniería Genética y Biología Molecular in Buenos Aires, Argentina, has focused on the optimization of several experimental parameters in order to successfully recover the memory response to *T. cruzi* infection in several patients at different stages of the disease (*manuscript in preparation*). In regards to steps 2 and 3, they have been extensively implemented in our laboratory. We have demonstrated the elucidation of T cell specificity using positional scanning peptide libraries in combination with *in silico* analysis with protein databases (biometrical analysis). A number of studies with clones of known specificity has been used to develop the methodology and revealed that the known antigens for most clones rank among the top 50 predicted stimulatory peptides, reviewed in[4]. Furthermore, as shown in table 1, the methodology was successfully utilized for clones of unknown specificity.