A COMPASS to Navigate Oceanic Datasets

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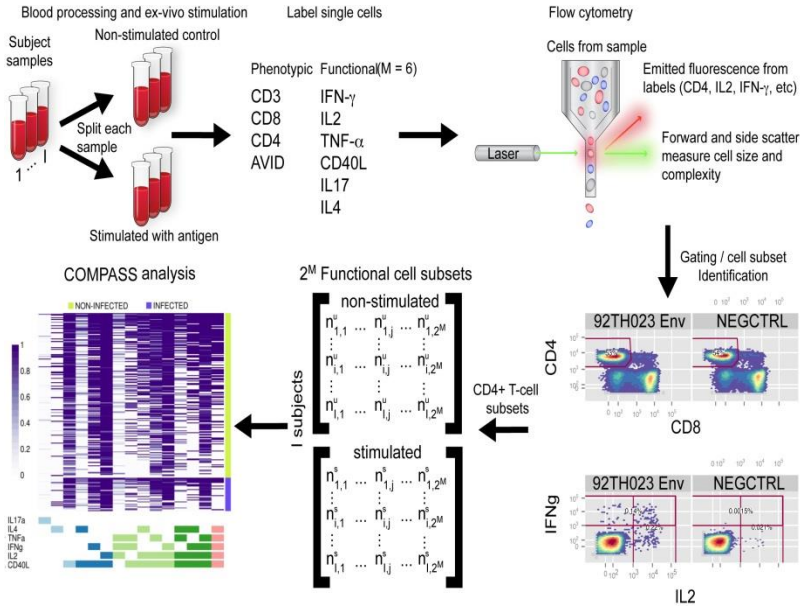

Overview of an ICS experiment and COMPASS analysis. COMPASS outputs heatmap of posterior probabilities that the corresponding cell-subset (column) exhibits an antigen-specific response in the corresponding subject (row).

Image provided by Dr. Lynn Lin.

T cell responses that are generated in vivo by antigen exposure can be amplified ex vivo upon incubation of T-cells with the same antigen. These antigen-specific T cell responses can vary drastically in their quantity and quality, measured by the combinations of cytokines that are produced. These variations depend on the antigen as well as on an individual's characteristics. Such variations make the study of the human immune system fascinating and challenging at the same time. A large number of possible combinations of cytokines produced by antigen-specific T cells complicate the analysis of large data sets generated to evaluate immune responses. As scientists, we should not discriminate between different subsets based on our preference but we should carefully look at all of them.

Customized tools are needed to do so in the most unbiased and reproducible way possible. Although a number of tools are available for flow cytometry data analysis, very few are designed specifically for high-throughput analyses. Most importantly, none of them is dedicated to characterize the quality of the cytokine response. Things are about to change. In fact, in a study published last month in Nature Biotechnology, Dr. Lynn Lin from the Vaccine and Infectious Disease Division (VIDD) at Fred Hutch reported the results obtained by analyzing three sets of data using a new tool

named COMPASS. COMPASS allows running qualitative analyses of cytokine combinations produced upon in vitro stimulation by specific subsets of cells.

The first data set was obtained from the RV144, a phase III clinical trial testing safety and efficacy of an HIV vaccine, which demonstrated a 31% vaccine efficacy. This dataset provided two benefits: first, it was possible to compare the results with previous analyses of the same data, and second, to correlate the results with trial outcome. The results from COMPASS not only showed increased sensitivity and specificity in discriminating between placebo and vaccine recipients as compared to two previously used methods, but also led to the identification of two polyfunctional cell subsets whose presence correlated with HIV protection in vaccinees.

The second data set compared cytokine response to TB-specific peptides in tuberculosis (TB)-infected versus uninfected subjects. Again, the use of COMPASS allowed for a better identification of the TB infected individuals. Furthermore, it identified antigen-specific subsets of cells in TB-infected subjects that secreted cytokines other than IFN-gamma, which is the cytokine measured for TB diagnosis. The reported results suggest measuring more cytokines can lead to more sensitive assays to identify TB infection.

The last data set analysis consisted of the comparison of two groups of individuals receiving the same vaccination regime, but at different doses. While the primary study showed no dose-specific differences, the use of COMPASS detected a reduction in one of the cell subsets when a higher dose of immunogen was used.

Collectively, the three analyses presented showed that using COMPASS to examine not just the quantity but also the quality of antigen-specific T-cell responses can increase specificity and sensitivity and lead to novel discoveries missed by traditional approaches. In times of high throughput data analyses, COMPASS can point us in the right direction!

Lin L, Finak G, Ushey K, Seshadri C, Hawn TR, Frahm N, Scriba TJ, Mahomed H, Hanekom W, Bart P-A, Pantaleo G, Tomaras GD, Rerks-Ngarm S, Kaewkungwal J, Nitayaphan S, Pitisuttithum P, Michael NL, Kim JH, Robb ML, O'Connell RJ, Karasavvas N, Gilbert P, C De Rosa S, McElrath MJ, Gottardo R. 2015. COMPASS identifies T-cell subsets correlated with clinical outcomes. Nat Biotechnol. DOI: 10.1038/nbt.3187. Epub ahead of print.