Laboratory Services
Important Test Announcement

T CELL ACTIVATION PANEL COMPLETE

New Test Code: TACPP **Live Date:** 12/18/2025

Methodology: Flow Cytometry
Performed: Monday - Friday
Turnaround Time: 72 hours
Specimen Required:

- **Collect:** EDTA (Preferred), Sodium Heparin
- **Specimen Preparation:** Do not centrifuge, do not refrigerate
- **Stability:** Whole blood (EDTA): 48 hours, ambient temperature. Whole blood (Sodium Heparin): 48 hours, ambient temperature.
- **Storage/Transport/Temperature/Conditions:** Transport Whole Blood EDTA and Sodium Heparin at ambient temperature. Do not refrigerate.
- **Unacceptable Conditions:** Wrong collection tubes, sample out of stability, refrigerated samples
- **Comments:** TACPP will include the TBNK test.

Clinical Utility:
Assessment of T cell activation using a variety of markers, including HLA-DR, CD38, and CD5 in CD4+ and CD8+ T cells, offers significant clinical utility as a real-time diagnostic and prognostic tool in a variety of contexts, including viral infections, autoimmunity, and immune dysregulation, specifically T cell dysregulation. These cellular markers are relevant in diagnosing and monitoring systemic inflammation and discriminating between a T cell-mediated pathology vs. other non-T cell-mediated inflammation (e.g., sepsis). This panel can also provide value as a prognostic indicator, in the context of serial monitoring, for disease outcomes and/or treatment response. These markers with co-expression data can provide insight into the activation state and functional aspects of T cells in disease contexts, and can be correlated with other useful biomarkers, such as sIL2R and CXCL9, among others.

HLA-DR is an MHC class II molecule that is expressed on human T cells when they are activated. CD38 is a multifunctional transmembrane ectoenzyme (NADase) that acts as both a cell surface receptor and a critical modulator of cellular metabolism. CD38 is involved in calcium signaling, which is vital for the initiation of T cell activation, proliferation, and cytokine production. While moderate (++) CD38 expression is part of a normal immune response, persistent high (+++) expression of CD38, especially in conjunction with HLA-DR, is associated with chronic immune stimulation leading to T cell exhaustion and functional dysregulation in chronic infections, malignancy, and T cell dysregulation. The T cells that express CD38+++ have impaired killing potential and higher apoptotic sensitivity. CD38 can also interact with its counter-receptor, CD31, on endothelial cells, to facilitate T cell adhesion and migration to sites of inflammation.

The co-expression of high levels of HLA-DR and CD38 on T cells is a reliable flow cytometry-based biomarker for systemic immune activation and is strongly correlated with clinical measures of inflammation and disease severity across various hyperinflammatory and immune dysregulation disorders. It helps distinguish effective, transient immunity from a pathological, persistent immune dysregulation.

It is important to note that CD38 is a dynamic marker with high expression on T cells at birth to maintain naïve T cells in a quiescent, metabolically dormant state to avoid unnecessary activation. CD38 expression, under normal physiological circumstances, reaches its lowest baseline levels in healthy children and adolescents as they age, as well as in young adults. In the aging and elderly population, CD38 expression can increase due to chronic antigen exposure and inflammaging, and T cell exhaustion. At any age, CD38 expression is rapidly upregulated in response to acute immune challenges, viral infections, T cell dysregulation, and even vaccination.

CD5 is a transmembrane glycoprotein constitutively expressed on the surface of virtually all T cells from early development through maturity, serving as a key marker to identify T cells. Its expression level is dynamically regulated and functions primarily as a negative regulator of T cell receptor (TCR) signaling, helping to fine-tune immune responses and prevent autoimmunity. While generally inhibitory in nature, the specific functional outcome of CD5 signaling is complex and context-dependent, sometimes promoting cell survival or influencing cytokine profiles. In normal physiological states, CD5 is uniformly expressed across naive, central memory, and effector memory T cell subsets in the peripheral blood. CD4+ T cells generally express higher baseline levels of CD5 than CD8+ T cells. Upon acute T cell activation in the secondary lymphoid organs, CD5 expression levels typically increase, correlating with heightened activation markers and effector function in these organs. CD5 may have a complex role in immune tolerance. In the tumor microenvironment (TME), T cells with lower CD5 expression are often associated with enhanced cytotoxic activity and a better response to immune checkpoint blockade (ICB) therapy, as the lowered CD5 threshold allows stronger anti-tumor responses.

In EBV infection, the concurrent expression of high levels of CD38 (i.e., CD38++/+++) along with a "down-regulation" or partial "loss" of the CD5 on expanded CD8+ T cells is a notable and diagnostically significant immunophenotypic finding. The specific immunophenotype (CD5 down-regulation and bright HLA-DR/CD38 co-expression on CD8+ T cells) is strongly associated with EBV-HLH, which is distinct from typical infectious mononucleosis (IM). Studies have found that while highly activated T cells (expressing high CD38 and HLA-DR) are present in both IM and EBV-HLH, the subpopulation showing significant CD5 down-regulation is consistently observed in patients with EBV-HLH, but not typically in those with uncomplicated IM or in healthy controls. These T cells are often the primary cellular targets of the virus and represent a clonally expanded population of EBV-infected CD8+ T cells, which can sometimes lead to a misdiagnosis of T-cell malignancy due to their abnormal phenotype and monoclonality. The frequency of these specific T cells tends to decline in parallel with the patient's recovery and the reduction of serum ferritin levels (elevated ferritin being a marker of HLH activity), highlighting their potential as a valuable tool for monitoring the progression and treatment response of EBV-HLH.

CD5 normally acts as a negative regulator of T cell activation, helping to maintain immune homeostasis. It’s down-regulation in the context of severe, persistent EBV infection and hyperactivation (CD38+++) suggests a mechanism where the normal regulatory “brakes” on T cell activity are lost, contributing to the uncontrolled immune response seen in HLH.
This assay includes assessment of these markers, not just on total CD4+ and CD8+ T cells but also in memory (CD45RO+) CD4+ and CD8+ T cell subsets.

In addition to measuring T cell activation status, this assay incorporates assessment of HLA-DR on CD14+ monocytes. MHC class II is constitutively expressed on monocytes, which can act as antigen-presenting cells (APCs) to T cells. Loss of HLA-DR expression on monocytes and/or a reduced frequency of monocytes expressing HLA-DR can be associated with a state of “immune paralysis." This phenomenon is primarily observed in critically ill patients with severe systemic inflammatory responses (e.g., sepsis, septic shock, major trauma, severe infections, e.g., viral and fungal, advanced neoplasias). Persistently low monocyte HLA-DR expression is a strong prognostic indicator of poor clinical outcomes. Measuring monocyte HLA-DR helps differentiate between an initial hyper-inflammatory phase (SIRS - Systemic Inflammatory Response Syndrome) and the subsequent, potentially fatal, hypo-inflammatory or compensatory anti-inflammatory response syndrome (CARS). Monitoring monocyte HLA-DR levels allows for the identification of patients who might benefit from immunostimulatory agents (e.g. rIFN-gamma, GM-CSF), which can restore monocyte HLA-DR expression to reverse the immunosuppressed state.

Clinical Report:
This test will include adult or pediatric (based on age of patient) reference intervals within the report. In the report, absolute counts of the CD45+ ALC will be provided along with % and absolute counts of T cell subsets (CD3+, CD4+ and CD8+ T cells), CD19/20+ B cells, and total and cytotoxic NK cells (i.e., lymphocyte subsets), in addition to the relative distribution (%) of T cell subsets expressing the above-mentioned activation markers (HLA-DR, CD38, CD5) [absolute counts of these T cell activation markers + subsets will not be provided as these are calculated values and affected by total CD4+ and/or CD8+ lymphopenia or lymphocytosis] and the proportion (%) and median fluorescence intensity (MFI; surrogate for amount of protein) of CD14+ monocytes expressing HLA-DR. A detailed interpretation of the results and their significance will be provided with the report.

If you have any additional questions about **T Cell Activation Panel Complete**, please refer to the Laboratory Test Directory or call Client Services at 614-722-5477.