



T cell profiling in post-acute infection syndromes (PAIS)

EXECUTIVE SUMMARY

Post-acute infection syndromes are clinically heterogeneous and lack reliable diagnostic biomarkers. Patients can display persistent T cell activation, altered T cell subsets or impaired T cell function. Profiling T cell phenotype, exhaustion and antigen-specific cytokine responses may help characterise immune dysregulation in PAIS.

POST-ACUTE INFECTION SYNDROMES

Post-acute infection syndromes (PAIS) are a group of persistent or relapsing conditions that develop after the acute phase of an infection and cannot be explained by another identifiable cause.^{1,2} They can follow viral, bacterial, fungal or protozoal infections, including SARS-CoV-2, influenza, Epstein–Barr virus, *Coxiella burnetii* (Q fever), dengue, chikungunya and *Giardia lamblia*. Long COVID, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and post-treatment Lyme disease syndrome are among the best-described examples.^{2,3} Although their infectious triggers differ, these conditions share persistent health effects and a substantial impact on daily life.

Patients commonly experience disproportionate fatigue, post-exertional malaise, cognitive difficulties, pain, unrefreshing sleep and flu-like symptoms. The pattern and severity can fluctuate, with illness lasting from months to years and ranging from mild disruption to profound impairment. Despite the scale of the problem, with tens of millions of people estimated to be affected by ME/CFS and cumulative estimates of around 400 million people affected by Long COVID worldwide, diagnosis remains largely based on exclusion.^{4,5} Overlapping symptoms, variable case definitions and the absence of reliable biomarkers can delay diagnosis, while current care is focused mainly on symptom management.

The biological mechanisms underlying PAIS are not yet fully understood and are likely to differ between patients. Proposed contributors include persistent antigen exposure or reactivation of latent viruses, autoimmunity, chronic inflammation, altered gut–immune signalling, endothelial dysfunction and impaired cellular energy metabolism.⁶ These pathways may interact, creating sustained immune dysregulation after the initial infection has resolved. T cell abnormalities have also been reported across PAIS, including persistent activation, changes in T cell subsets and impaired function.^{7–9} In some settings, prolonged antigenic stimulation can contribute to T cell exhaustion, with reduced cytokine production and cytotoxic activity, increased expression of inhibitory receptors and metabolic dysfunction. These findings support closer examination of T cell phenotype and function in PAIS.

IMPORTANCE OF T CELLS IN PAIS

T cells are central to the adaptive immune response. CD4⁺ T cells coordinate immune activity, while CD8⁺ T cells recognise and eliminate infected cells. Following infection, memory T cells remain available to respond to previously encountered antigens. Persistent changes in these populations can therefore provide evidence of continued immune activation or altered immune regulation after the acute infection has resolved.



Prolonged antigenic stimulation can drive T cells towards exhaustion, a distinct state of progressive dysfunction rather than a temporary reduction in activity. Exhausted T cells show impaired proliferation, cytokine production and cytotoxicity, limiting their ability to clear infected cells.¹⁰ They can also co-express inhibitory receptors such as PD-1, LAG-3, TIM-3 and TIGIT; expression of CD39 is associated with more terminal dysfunction.¹¹ These functional changes are accompanied by reduced glycolytic capacity, impaired oxidative phosphorylation, mitochondrial dysfunction and restricted nutrient use.

Evidence of T cell dysregulation has been reported in both post-acute COVID syndrome (PACS, also known as Long COVID) and ME/CFS. PACS studies have described increases in activated, cytotoxic and memory CD4+ and CD8+ T cells, together with variable changes in naïve and regulatory populations.^{9,12,13} In ME/CFS, studies have reported altered CD8+ differentiation, as well as increased CD8+ mucosal-associated invariant T cells in some severely affected patients.¹⁴

More recent work suggests that T cell abnormalities may extend beyond the circulation. In Long COVID, increased frequencies of tissue-homing CD4+ T cells and a Th2 bias have been reported,¹⁵ while T cell-targeted positron emission tomography has shown increased T cell activation in several tissues, including the gut wall and spinal cord, where signal was associated with persistent Long COVID symptoms.¹⁶ Single-cell profiling of Long COVID with ME/CFS features has also identified reductions in naïve CD4+ and CD8+ T cells, regulatory T cells, mucosal-associated invariant (MAIT) cells and $\gamma\delta$ T cells, alongside expansion of effector populations and transcriptional evidence of exhaustion.⁹

T cells may also participate in self-sustaining inflammatory loops with B cells, monocytes and macrophages.^{6,17} T cell-derived IFN- γ can activate monocytes and macrophages, which in turn stimulate T and B cells; antibodies can activate myeloid cells; and CD40L on activated T cells can engage CD40 on B cells and monocytes. These reciprocal interactions may help maintain inflammation and impaired T cell responses in some patients.

Overall, current evidence supports T cell dysregulation in people with PAIS but does not define a single profile shared by all conditions or individuals, with studies supporting the assessment of responses beyond cell counts alone. Relevant measures include activation of memory T cells by infection-derived antigens and parallel detection of cytokine responses, which provide readouts of antigen-specific function and inflammatory signalling. Results can then be evaluated against a healthy-donor reference range. Measuring several cytokine responses in parallel at single-cell level can help characterise the functional pattern of the antigen-specific T cell response in PAIS.

ADVANCING T CELL PROFILING IN PAIS WITH VIRAXIMMUNE™

ViraxImmune™ is an innovative cellular immunology platform in development. Its current development focus is the assessment of cellular immune dysfunction associated with PAIS, where it is being evaluated as a potential aid to clinical assessment. Patient-derived peripheral blood mononuclear cells (PBMCs) are isolated from a blood sample and exposed to selected pathogen-derived peptide pools under standardised laboratory conditions. Antigen-specific T cell responses are then assessed using FluoroSpot technology to measure selected cytokine responses following antigen stimulation. The resulting cellular-response data are analysed within a composite analytical framework being developed for ViraxImmune™.

In preliminary pilot data, ViraxImmune™ differentiated PAIS samples from healthy controls, with 88% specificity and a 92% positive predictive value ([Read the full announcement here](#)). These



findings have not yet been clinically validated and are being evaluated in larger ongoing studies. Further studies are currently underway to contribute to the UK clinical-performance dataset for ViraxImmune™ in PAIS; investigate memory T cell-driven immunity in patients with chronic fatigue symptoms following SARS-CoV-2 exposure; and support assay development, optimisation, reference-range establishment and preliminary performance evaluation using fresh human biological samples.

The assay remains in development and is not currently available for clinical diagnostic use. ViraxImmune™ is being developed to provide an additional measure that may support clinical assessment and patient stratification, and is not presented as a standalone diagnostic. The clinical utility and performance of ViraxImmune™ remain subject to ongoing validation and applicable regulatory requirements.

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