Post-Acute Infection Symptoms Webinar Questions and Answers

Responses are provided by Drs. Anthony Komaroff and Robert Dantzer unless otherwise noted.
Dr. Julie Williams provided additional responses to selected questions which are labeled below.

Disease Mechanisms and Persistence

1. **How can non-infectious ME be explained and how can Post-Exertional Malaise be understood in this context, given that it might be different from 'persistent severe flu' ?**

   The symptoms triggered by an infection are a protective response to a vital threat: the symptoms change behavior in such a way as to preserve the energy needed to fight the infection. There is evidence that this same protective response may be triggered by major physical trauma. Furthermore, many cases of "non-infectious" ME may be caused by an infection that has not been diagnosed.

2. **What causes increases in prostaglandins in these diseases?**

   Prostaglandins are molecules produced by innate immune cells. They are part of the arsenal of molecules produced during inflammation.

3. **Are there any speculations as to why sickness symptoms persist in some individuals while others are able to fully recover?**

   We argued that a variety of different forces can cause the symptoms to persist in some people, as outlined in detail in a recent paper (Komaroff AL, Dantzer R. Cell Rep Med. 2025;6(8):102259).

   Additional response from Dr. Williams: This is an insightful question. A similar question can be asked of why some people get cancer and others do not, despite being exposed to high risk factors (such as smoking, for example). In some cases, inherited genetic mutations (BCRA1 or 2) can lead to increased risk of breast or other cancers. GWAS, metabolomics, and other types of bioinformatic approaches have attempted to identify risk factors in ME/CFS patients, but so far, no single factor that I am aware of has emerged from these studies. However, a common theme among these is abnormalities in immune and metabolic profiles. Whether these are causal or a result of the disease is not yet well understood.

4. **Dr. Komaroff suggested 3 categories of reasons why sickness symptoms may persist beyond acute infection. Might different patients' symptoms be persisting for different reasons, and what would that mean for future research and potential treatments?**

   That is exactly the point: the underlying pathology includes a group of different aberrations—mitochondrial dysfunction, redox imbalance, autonomic dysfunction—that reinforce each other. In any given individual, one may be more important than it is in another individual.

   Note: The same question comes back in different guises. Individual differences in the risk of developing PAIS can arise from many different factors that relate to individual differences in the

intensity and duration of the immune response to the microbial pathogen or to individual differences in the sensitivity of the cellular targets to the stress imposed on them by the immune response.

Additional response from Dr. Williams: This is very speculative, but what could be underlying these "different reasons" is nuclear restructuring. There is a growing body of work that shows non-cell autonomous changes in the way nuclear chromatin is folded, which would change the way genes are transcribed in that cell. In other words, a virus that infects one cell type can have effects on cells that are not infected. How it does this, and whether this is attributed to secreted factors within the host is unknown.

5. **If IACCI encompasses MS, as suggested, then what does that say about using it as a differentiating patient population when attempting to distinguish fatigue from ME in specific studies?**

   Dr. Komaroff thinks that post-acute infection syndromes, or PAIS (like ME/CFS and Long COVID), are just one example of an even broader category: infection-associated chronic conditions (IACC). The broader category of IACCI includes MS, lupus, stomach ulcers and cancers (which can be caused by a bacterium), and other illnesses. These other illnesses do not always share core symptoms of PAIS like PEM, brain fog, disrupted sleep, etc., and these other illnesses can include symptoms like paralysis, blindness, kidney failure, etc., that are not seen in PAIS. (Note: you can generalize from MS and lupus to other autoimmune diseases. All these diseases involve an activation of the immune system in one way or another, which means that this immune response won't remain local, at the site at which it develops initially, but will propagate to other organs including the brain, just like in the case of a microbial infection).

6. **I understand tryptophan hydroxylase is inhibited and should lead to low serotonin. Most ME/CFS patients I see have excess serotonin. How would you explain this?**

   One excellent paper shows that, in Long COVID, serotonin levels in the plasma (and in platelets) are low, due to impaired gut absorption of serotonin and alterations in the tryptophan-serotonin-kynurenine pathways. However, circulating serotonin (which is mainly coming from the gut) has no influence on brain serotonin, as serotonin cannot pass through the blood-brain barrier.

   Similar systematic studies of all aspects of serotonin metabolism have not been done in ME/CFS. And there are no definitive human studies of serotonin metabolism where the action is: in the central nervous system.

   Additional response from Dr. Williams: I would consider the time-of-day that you are taking measurements. Plasma serotonin can fluctuate with time-of-day or with mealtimes. I expect this would be abnormal in ME/CFS patients, so it might depend on what you are using as a reference to qualify serotonin level as "excess".

7. **Would free-circulating mtDNA cause the same effects as a virus? Regarding both, which could be most likely to raise an immune response, including an autoimmune response?**

Indeed, free-circulating mtDNA (and, more generally, mitochondrial damage-associated molecular patterns, or mtDAMPs) are often regarded by the immune system as "foreign", triggering an inflammatory response. A good reference to learn more about this is: https://pubmed.ncbi.nlm.nih.gov/37001140/.

Free-circulating mtDNA surely can *modulate* the severity of an autoimmune disease. We are not sure there is persuasive evidence that it can *trigger* an autoimmune disease.

8. **Has anyone studied the common mechanisms of post-infection events across different infections?**

   One of the goals of our paper was to encourage just such studies. We think it is quite possible, but unproven, that there will be many similarities in the pathophysiology of PAIS initiated by different infectious agents.

Triggers, Viral Persistence, and Immune Dysfunction

1. **Could mRNA vaccines be a trigger?**

   Theoretically, any type of vaccine could trigger a dysfunctional immune response in some people. Fortunately, studies of millions of people given various vaccines show that this is rare, and that the benefit from giving vaccines outweighs the risks.

2. **Given research suggesting that COVID may persist in the body's tissues, which treatments are of interest for clearing these reservoirs in Long COVID patients?**

   It is clear that the nucleic acids and antigens of the SARS-CoV-2 virus can persist in tissues for a long time. Whether living, replicating virus persists is less clear, and antiviral treatments generally affect the ability of living viruses to replicate. Indeed, several studies have failed to find that antiviral treatments of Long COVID reduce symptoms.

   However, people who have received antiviral treatment for *acute* COVID—when the virus definitely is replicating—are less likely to develop Long COVID than similar patients who did not receive antiviral treatment.

3. **Could ME/CFS involve premature replacement of resident microglia by circulating monocytes, potentially driven by B-cell autoimmunity? If so, could early anti-CD19/BCMA CAR-T therapy interrupt this process before persistent neuroimmune dysfunction develops?**

   Circulating monocytes have the potential to replace macrophages in brain border regions, but probably don't have the potential to replace microglia in the brain parenchyma.

   CAR-T cell therapy to curtail B-cell-driven autoimmunity might someday prove beneficial, when the evidence is stronger that autoantibodies are an important cause of an individual's symptoms. We are not aware of any evidence yet that would justify the use of CAR-T therapy for ME/CFS or Long COVID at the current time, however.

4. **Is there reason to believe that exertion during acute illness plays a role in the development of PAIS and persistent sickness behavior?**

   No evidence that we are aware of.

   Additional response from Dr. Williams: I am not aware of any evidence that supports this. However, it is documented across species that sleep during an infection can benefit recovery; if you delay sleep you can delay recovery.

5. **What is the connection with mast cell hyperactivation, and is there a significant link between the two?**

   Mast cell activation has been documented in some people with PAIS and may be contributing to the symptoms in those people. This question deserves much more study.

Brain, Neuroinflammation, and Neurological Effects

1. *I understand the concerns raised here given the history of how our illness has been treated. At the same time, evidence suggests understanding what's going on in the brain and the talk between the immune system and the brain is going to be crucial for curing this illness so I am very grateful for this webinar.*

   Is there any possibility of a webinar relating these topics to the DecodeME results, which point to the brain and immune system?

   This is a great suggestion, and the webinar organizers will consider this for a webinar in the future.

2. **What is your opinion on 'post-concussion syndrome' in the brain after rigorous or prolonged cognitive activity in people with cognitive problems from ME/PAIS, including metabolic collapse in the brain?**

   An illness similar to PAIS can follow major physical trauma (including trauma to the head and other parts of the body). It is possible that similar underlying pathophysiology is triggered by such trauma. This requires much more study.

3. **For patients with Long COVID who want to assess neuroinflammation through imaging, who would they need to see—a neurologist who specializes in this area?**

   Techniques to image neuroinflammation are improving. Neurologists generally order such tests, and radiologists conduct the tests. Dr. Michelle James at Stanford is doing some excellent research in this area and applying it to ME/CFS and Long COVID; see: Illuminating proinflammatory myeloid cells with PET tracers targeting GPR84

4. **Can you discuss the interaction between PAIS and aging? Can persistent or recurrent viral illnesses underlying PAIS drive age-related diseases, including Alzheimer's and Parkinson's disease, through protein aggregation, mitochondrial stress, or other mechanisms?**

Persistent viral infection (or persistent reservoirs of viral nucleic acids and antigens) can trigger persistent inflammation. Ongoing inflammation, in turn, appears to be an important part of many age-related diseases. There have been only a few studies of markers of accelerated aging in people with PAIS.

5. **Could targeted splenic ultrasound stimulation serve as a noninvasive test to predict which ME/CFS patients might benefit from vagus nerve stimulation, based on measurable immune and symptomatic responses?**

   Splenic ultrasound stimulation and vagus nerve stimulation both activate the anti-inflammatory cholinergic reflex described by Kevin Tracey. Both techniques have shown promise in alleviating symptoms in some inflammatory diseases. We don't know yet if either technique will prove valuable in people with ME/CFS or Long COVID who have evidence of ongoing low-grade systemic inflammation and/or neuroinflammation.

6. **Could targeted splenic ultrasound stimulation serve as a noninvasive test to predict which ME/CFS patients might benefit from vagus nerve stimulation, based on measurable immune and symptomatic responses?**

   Same as answer to question #5, above.

Treatments, Trials, and Supplements

1. **Which ME/CFS treatment trials are most exciting at the moment?**

   They are all exciting. Our hypothesis would hold that treatments that target various aspects of neuroinflammation would be most promising.

2. **Given the findings from the pilot daratumumab study from Norway in ME/CFS patients, what are your thoughts on daratumumab and other CD38 drugs?**

   The small (10 people) study you refer to suggested that this treatment may help some people, presumably those whose symptoms are generated in part by autoantibodies. However, much larger, controlled trials are necessary to test this possibility.

3. **From a clinical perspective, does supplementation with creatine, fish oil, magnesium threonate, or urolithin A change or reduce symptoms?**

   We are doubtful of the efficacy of these relatively non-specific supplements. There are a few studies indicating fish oil may have some benefit in this illness and others characterized by inflammation.

4. **Are there actual plans to push forward this particular research in other models?**

   There are discussions about how best to approach this hypothesis in animal models, particularly rodents.

Additional response from Dr. Williams: There are several investigators (myself included) who use the Drosophila fruit fly model; others use mouse and C. elegans worm or other genetic models to investigate mechanisms underlying sickness sleep or other aspects of infection/stress-induced behavior. The goal is to identify common evolutionarily conserved signaling pathways that cause ME/CFS-like symptoms. As a complex disease state, these reductionist approaches are critical for advancing understanding of PAIS.

5. *Several presentations referenced oxidative stress, including a Stanford paper, 'Oxidative stress is a shared symptom of ME/CFS and Long COVID,' and data on the use of NAC, a precursor to glutathione, to mitigate oxidative stress.*

   Based on the research, do NAC/glutathione seem like strong therapeutic candidates for further research?

   There is abundant evidence of increased oxidative stress (redox imbalance) in people with both ME/CFS and Long COVID. Therefore, treatments directed at this abnormality seem worth trying. However, many illnesses in which redox imbalance has been documented have not responded to various antioxidant treatments.

6. **Do NSAIDs or steroids reduce symptoms in CFS patients? If persistent inflammation is contributing to symptoms, this seems like a logical treatment option to test.**

   Corticosteroids have not proved successful, and long-term use carries clear risks. Anecdotally, NSAIDs appear to reduce pain in many (but not all) patients, but broader benefits have not been demonstrated thus far.

   Dr. Komaroff thinks that various aspects of neuroinflammation, rather than systemic inflammation, may be a better target. Dr. Dantzer thinks the symptoms are more likely due to the cellular damage caused by neuroinflammation, damage that is hard to heal, especially when it involves mitochondrial damage.

   Additional response from Dr. Williams: I am not sure, but my guess is that the target of NSAIDs and mechanisms of action are too narrow, and possibly too mild.

Patient Care, Research Support, and Medical Framing

1. **How can the patient and caregiver community, and nonprofits already advocating, further support research to speed it up?**

   The NIH/NINDS solicited and received a detailed plan for further research on ME/CFS, from leaders in the field. Funding of the specific types of research mentioned in that plan should be strongly encouraged—by contacting members of Congress.

2. **Based on the presentations, what are your recommendations for countering the mind-body conceptualization of post-viral conditions as psychosomatic, given that many clinicians are ill-informed about current pathophysiological findings?**

The word “psychosomatic” is understood by many people to mean that there is nothing wrong in the body that could explain the symptoms—that the symptoms are just imagined. If that is what someone means when they say PAIS are “psychosomatic”, then we recommend telling that person (clinician, family member, friend, work colleague) that there are, in fact, tens of thousands of peer-reviewed articles published in scientific journals that find multiple underlying abnormalities that could be causing the symptoms in various PAIS.