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Controversies in Multiple Sclerosis

Targeting EBV is a viable therapeutic strategy in MS: YES

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In January, 2022 two landmark publications appearing in *Science*1 and *Nature*,2 within 9 days of each other, illuminated a critical role of the immune response to Epstein-Barr virus (EBV) in multiple sclerosis (MS). Ascherio's group at the Harvard School of Public Health studied blood specimens from over 10 million US military members collected from 1993 to 2013. There were 801 cases of MS and 800 were positive for anti-EBV antibodies. Thirty-five of the 801 with MS, entered the military negative for anti-EBV antibodies, and 34 of the 35 became EBV positive *before* the onset of MS.[1] Measurements of serum neurofilament light chain increased around the time of EBV infection. The authors concluded that infection with EBV was the leading cause of MS.

Within days of the online publication of the *Science* paper,[1] a paper from our Stanford group was accepted at *Nature*.[2] Oligoclonal immunoglobulin in the cerebrospinal fluid (CSF) had been studied with electrophoresis with the first demonstration in a patient with Subacute Sclerosing Panencephalitis in 1959.[3] Oligoclonal immunoglobulin in the CSF of MS patients remains a cornerstone of evaluation of an individual for MS. The presence of such oligoclonal bands in the CSF is highly supportive of a diagnosis of MS.[2]

The Stanford group studied plasmablasts and B cells in the CSF of MS patients, investigating clonal antibodies and their immunoglobulin sequences that had undergone somatic hypermutation in the cerebrospinal fluid. We showed that there was a region of molecular mimicry between a molecule in the myelin sheath, GlialCAM, and a region of the EBNA-1 transcription factor. The anti-GlialCAM antibody had undergone somatic hypermutation from its germline sequence, increasing its binding affinity in the cross-reactivity with EBNA-1. The affinity of the anti-GlialCAM antibody for EBNA-1 increased further—more than 50-fold—after a post-translational modification (phosphorylation) near the region of mimicry.

Another transcription factor, myocyte enhancer factor 2b (MEF2b), was also bound by the same clonal antibody. Like EBNA-1, MEF2b is involved in maintaining the latency of the EBV virus, inhibiting it from going lytic.[3] Four other publications spanning 2019 to 2025[4–7] showed that within a 47 amino acid linear stretch of EBNA-1, there were three regions of molecular mimicry that individually increased the odds ratio for getting MS to approximately 10-fold.

Next to the region of mimicry to GlialCAM, there was a region of mimicry to aB crystallin (CRYAB).[6] CRYAB is a guardian molecule protecting the brain from neuroinflammation.[4,6,7] Next to the region of mimicry between CRYAB and EBNA-1 is a region of mimicry to a chloride channel molecule anoctamin-2 (ANO-2).[5]

In a collaboration with the scientists at the Karolinska, the Stanford group and the Swedish group studied 650 MS patients and 661 matched population controls. In the 2025 publication,[7] we showed that antibody responses against EBNA1, GlialCAM, CRYAB, and ANO2 are elevated in MS patients. In fact, in individuals carrying the main risk allele HLA-DRB1*15:01, and combinations of HLA-DRB1*15:01 with anti-EBNA1 and anti-GlialCAM antibodies, or HLA-DRB1*15:01 with anti-EBNA1 and CRYAB antibodies, or HLA-DRB1*15:01 with anti-EBNA1 and ANO-2 antibodies, there was a significantly increased risk of MS.[7] The effects of these regions of mimicry between EBNA-1 and molecules involved in the pathogenesis of MS are additive. These discoveries provide a set of potential biomarkers for some of the therapeutic strategies that might emerge from this work.

Thus, within 47 amino acids of each other in the linear sequence of EBNA-1 are three molecular mimics with proteins that play known pathophysiologic roles with MS. These discoveries enable various therapeutic strategies that might transform treatment of MS, or even eliminate disease.

Therapeutic strategies that emerge from these recent studies on EBV and MS

We concluded reference 2 writing, "Our results provide a mechanistic link for the association between MS and EBV and could guide the development of new MS therapies." In reference 4, we mention that the work from Ascherio and colleagues provides an opportunity to potentially eliminate MS with an effective vaccine to EBV.

In fact, the development of vaccines against vaccine has reached the clinic. There are several clinical trials targeting various EBV components. Vaccines included an mRNA construct being tested in healthy individuals, and in those with MS NCT06735248, and an EBV gp350-Ferritin nanoparticle vaccine being tested in healthy humans NCT04645147 under the auspices of the National Institutes of Health (NIH). Another vaccine under investigation is a nanoparticle vaccine targeting gH, gL, and gp42, as well as an antigen derived from gp350 under the auspices of OPKO and Merck NCT06655324.

Anti-virals targeting EBV are another promising modality. In fact anti-viral trials for individuals with MS are underway. The Australians commissioned a study group to repurpose approved drugs with anti-viral activity.[8] The Australian group is planning to start clinical trials in the near future. In Norway, there is an ongoing trial with tenofovir alafenamide fumarate (TAF) in individuals with MS. (https://www.helse-bergen.no/en/neuro-sysmed-english/clinical-studies-at-neuro-sysmed/ms–clinical-studies/taf-ms-1/)

Other approaches are being developed with autoantigen-specific chimeric T cells (CAAR-T cells) aimed at targeting the plasma cells making clonal antibody to GlialCAM, CRYAB, and ANO-2. Other approaches using biologics that engage T cells and that carry the antigens targeted by the cells making antibody to EBNA-1 mimics are also under development. These therapeutic approaches with vaccines, anti-virals targeting lytic EBV, cell therapies, and T-cell engagers provide the opportunity to eliminate multiple sclerosis, just as we eliminated poliomyelitis over three quarters of a century ago.

Data Availability Statement

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Declaration of Conflicting Interests

The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Steinman has filed patents on antigen specific approaches targeting EBNA-1 mimics GlialCAM, CRYAB, and ANO-2.

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