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New Landmark Nature Study Provides Long-Sought Mechanistic Link Between EBV and Multiple Sclerosis, Extending Findings from Recent Paper in Science That Identified EBV as the Leading Cause of Multiple Sclerosis

Aberrant Immune Response to EBV Protein Triggers the Immune System to Attack and Destroy Myelin, Leading to Onset and Progression of Multiple Sclerosis (MS)

Findings Reinforce Potential for ATA188 to Treat the Cause of MS by Specifically Targeting EBV-Infected B cells and Plasma Cells

Reinforces Recent Epidemiological Analysis in Science of >10 Million Individuals Over Two Decades Providing Compelling Evidence of Causality of EBV Infection and MS

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)-- Atara Biotherapeutics, Inc. (Nasdaq: ATRA), a leader in T-cell immunotherapy, leveraging its novel allogeneic Epstein-Barr virus (EBV) T-cell platform to develop transformative therapies for patients with cancer and autoimmune diseases, today lauded the second high impact study this month solidifying EBV as the primary driver of the development of MS. The paper, titled, “Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 and GlialCAM,” was published today in the journal *Nature.*

MS is a chronic neurological illness affecting an estimated 2.8 million people worldwide, including approximately 900,000 in the U.S. MS is driven by abnormally activated immune cells and subsequent inflammation which damages and ultimately destroys the protective myelin sheath surrounding nerve fibers in the central nervous system (CNS). While genetics and environmental factors play a role, it has long been postulated that EBV triggers the patient’s immune cells to erroneously attack myelin.

The *Nature* study adds to the known EBV-MS epidemiological connection by providing a mechanistic basis for how EBV infection can trigger the patient’s immune cells to attack self-tissue in the CNS. These findings validate molecular mimicry as one of the leading mechanisms of EBV-mediated MS, which occurs when fragments of the virus share sequence or structural similarities with certain brain proteins. The immune system may mistake these “self-proteins” for EBV. These new data reveal how EBV infection can drive the development of antibodies that target both EBV and CNS proteins, potentially leading to MS.

The researchers identified a type of antibody isolated from MS patients’ cerebrospinal fluid

(CSF), which strongly binds an EBV protein, EBNA1, and cross-reacts with the central nervous system protein GlialCAM. GlialCAM is a cell adhesion molecule expressed in a variety of brain cells, including oligodendrocytes that are responsible for producing myelin, as well as on the outside of myelin sheaths. This antibody cross-reactivity between EBV and self-proteins was found to result from molecular mimicry due to key similarities between GlialCAM and EBNA1. The group also demonstrated that immunization with EBNA1 in a mouse model of MS exacerbated the disease and generated a strong antibody response against GlialCAM and EBNA1, enhancing immune cell infiltration and demyelination that are two hallmark features of human MS pathology.

“EBV may be the only risk factor required to develop MS, given essentially 100 percent of people living with MS have been infected with EBV. Until now, we didn’t have a step-by-step account of how this drives the immune system to attack a person’s own myelin sheath,” said Lawrence Steinman, MD, Professor of Neurology and Neurological Sciences, Pediatrics and Genetics, Stanford University, and author of the study. “This new research fills in those gaps and provides clarity into how EBV infection can cause MS. New therapies that specifically target this link are already in development, including Atara’s ATA188 T-cell immunotherapy, which is actively enrolling a Phase 2 clinical study.”

The *Nature* paper complements findings from a second publication, “Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis,” recently published in the journal *Science*, and collectively provide new epidemiological and molecular data confirming the role of EBV in triggering and driving the pathophysiology of MS. The cohort-based study provided compelling epidemiological evidence that EBV infection precedes the onset of MS. The study analyzed 62 million serum samples and followed >10 million individuals in the U.S. military over a 20-year period (1993-2013), showing a 32-fold increase in the risk of MS after EBV infection. Out of the 801 MS cases identified, 35 were EBV negative at baseline with all but one becoming EBV positive before the onset of their MS, yielding a 97 percent seroconversion rate versus 57 percent among individuals who did not develop MS. Serum concentrations of neurofilament light chain (sNfL), a sensitive biomarker for nerve fiber damage, only increased after EBV infection, indicating that EBV infection preceded not only symptom onset but also the time of the first detectable pathological mechanisms underlying MS. Other viral infections, like CMV, were not found to increase the risk of MS and were ruled out as a contributing factor in MS development.

“These studies identify EBV as the leading cause of MS and provide a direct mechanistic link between the activation of the immune system caused by EBV, and the autoimmune myelin pathology observed in MS,” said AJ Joshi, MD, Chief Medical Officer at Atara. “Specifically, these new data further link MS to EBV-infected B cells and plasma cells, highlighting the role of EBV antigens, including EBNA1 protein, in the development of the disease. Importantly ATA188, Atara’s investigational MS therapy, targets key epitopes of these antigens, including EBNA1, with the hope of ultimately delivering a new treatment option for the millions of people currently living with MS. The actively enrolling Phase 2 EMBOLD study, with a formal interim analysis planned for Q2 this year, will be a major step toward that direction.”

The complete articles are available in digital format and can be viewed via the following links:

- https://www.nature.com/articles/s41586-022-04432-7

- https://www.science.org/doi/10.1126/science.abj8222

About Progressive Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, debilitating, and potentially disabling autoimmune disease of the central nervous system (CNS) that affects myelin, a protein that helps nerves in the brain and spinal cord communicate. There are an estimated 2.8 million people living with MS worldwide, with up to ~1.2 million living with progressive forms of the disease, marked by continuous clinical decline and worsening disability. While the exact triggers of MS are not fully established, inflammation driven by environmental and genetic factors is suspected. There is growing evidence that EBV, carried by more than 90 percent of the population that infects a particular type of immune cell called the B cell, may have a role in MS and in fact may be the only risk factor identified necessary to cause MS. With few treatment options available for progressive MS and the ability of these treatments to fundamentally alter disease progression, there remains a critical unmet need.

About Atara Biotherapeutics, Inc.

Atara Biotherapeutics, Inc. (@Atarabio) is a pioneer in T-cell immunotherapy leveraging its novel allogeneic EBV T-cell platform to develop transformative therapies for patients with serious diseases including solid tumors, hematologic cancers and autoimmune disease. With our lead program in Phase 3 clinical development and currently under review to support registration in Europe, Atara is the most advanced allogeneic T-cell immunotherapy company and intends to rapidly deliver off-the-shelf treatments to patients with high unmet medical need. Our platform leverages the unique biology of EBV T cells and has the capability to treat a wide range of EBV-associated diseases, or other serious diseases through incorporation of engineered CARs (chimeric antigen receptors) or TCRs (T-cell receptors). Atara is applying this one platform, which does not require TCR or HLA gene editing, to create a robust pipeline including: tab-cel in Phase 3 development for Epstein-Barr virus-driven post-transplant lymphoproliferative disease (EBV+ PTLD) and other EBV-driven diseases; ATA188, a T-cell immunotherapy targeting EBV antigens as a potential treatment for multiple sclerosis; and multiple next-generation chimeric antigen receptor T-cell (CAR-T) immunotherapies for both solid tumors and hematologic malignancies. Improving patients' lives is our mission and we will never stop working to bring transformative therapies to those in need. Atara is headquartered in South San Francisco and our leading-edge research, development and manufacturing facility is based in Thousand Oaks, California. For additional information about the company, please visit atarabio.com and follow us on Twitter and LinkedIn.

Forward-Looking Statements

This press release contains or may imply "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. For example, forward-looking statements include statements regarding: the development, timing, progress and prospects of ATA188 and clinical trials relating to ATA188, the potential benefits of ATA188, the safety profile of ATA188, the potential for ATA188 to treat multiple sclerosis, the potential market for ATA188, the mechanistic link between EBV and multiple sclerosis and the ability of ATA188 to specifically target such link. Because such statements deal with future events and are based on Atara's current expectations, they are subject to various risks and uncertainties and actual results,

performance or achievements of Atara could differ materially from those described in or implied by the statements in this press release. These forward-looking statements are subject to risks and uncertainties, including, without limitation, risks and uncertainties associated with the costly and time-consuming pharmaceutical product development process and the uncertainty of clinical success; the COVID-19 pandemic, which may significantly impact (i) our business, research, clinical development plans and operations, including our operations in South San Francisco and Southern California and at our clinical trial sites, as well as the business or operations of our third-party manufacturer, contract research organizations or other third parties with whom we conduct business, (ii) our ability to access capital, and (iii) the value of our common stock; the sufficiency of Atara's cash resources and need for additional capital; and other risks and uncertainties affecting Atara's and its development programs, including those discussed in Atara's filings with the Securities and Exchange Commission (SEC), including in the "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of the Company's most recently filed periodic reports on Form 10-K and Form 10-Q and subsequent filings and in the documents incorporated by reference therein. Except as otherwise required by law, Atara disclaims any intention or obligation to update or revise any forward-looking statements, which speak only as of the date hereof, whether as a result of new information, future events or circumstances or otherwise.

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