



REPLY TO RUPRECHT AND MAYER:

Unearthing genomic fossils in the pathogenesis of multiple sclerosis

David Kremer^a, Hervé Perron^b, and Patrick Küry^{a,1}

This Reply refers to the Letter by Ruprecht and Mayer titled "On the origin of a pathogenic HERV-W envelope protein present in multiple sclerosis lesions" (1). In their Letter, the authors confirm the specificity of the monoclonal antibody GN-MAb_03 (3B2H4) that we used to detect the pHERV-W ENV protein in multiple sclerosis (MS) lesions (2). We found that pHERV-W ENV is present in lesion-associated myeloid cells and may contribute to neurodegeneration in MS by driving microglia to attack myelinated axons. Our data provide a biomedical rationale for the results of a clinical phase IIb study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02782858) identifier NCT02782858) in which an anti-pHERV-W ENV monoclonal antibody termed temelimab was found to exert neuroprotective effects.

In their previous work (3) and in their current Letter, Ruprecht and Mayer address the genomic origin(s) of the ENV protein detected by GN-MAb_03. GN-MAb_03 had previously been shown to recognize pHERV-W ENV [originally named MSRV-ENV; GenBank sequence AF331500 (4)] which is identical to the recombinant ENV protein also used in our functional experiments. To date, no counterpart for the AF331500 sequence has been found in human genome databases, but nonubiquitous HERV elements are now known to exist, including in the HERV-W family (5, 6). Alternatively, somatic mutations might account for the observed pathogenic expression in MS, e.g., a potential recombination of transcripts from HERV-W loci homologous to AF331500, the ERVWE2 locus on chromosome Xq22.3, and another on chromosome

5p12, as suggested by Ruprecht and Mayer (3, 7). GN-MAb_03 detects the truncated or mutated full-length ENV protein encoded by the Xq22.3 locus. Importantly, GN-MAb_03 does not detect syncytin-1, another HERV-W ENV protein encoded by a partly defective HERV-W copy inserted at the ERVWE1 locus on chromosome 7 (8). Syncytin-1 is a "domesticated" HERV protein whose expression is restricted to placenta (9). In their Letter the authors propose that the HERV protein that we found to contribute to neurodegeneration in MS is encoded by the ERVWE2 locus and obviously not by ERVWE1.

However, a previous study revealed no evidence of nucleotide polymorphism lifting the stop codon in the Xq22.3 locus in MS (10). In this context, it is important to point out that currently available sequencing and annotation technologies are no reliable means to identify single HERV insertions as 8% of the human genome represents highly homologous sequences within multiple HERV families (5, 11). Therefore, alternative approaches aiming at identifying fixed or unfixed HERV copies need to be employed to track down nonubiquitous candidate loci and/or somatic rearrangements.

Even though within the framework of MS therapy an effective neutralization of pHERV-W ENV and thus treatment for neurodegeneration is becoming a reality, clarifying the origins of this deleterious protein is needed to understand whether the encoding DNA copy is infrequently inherited or de novo recombined in affected cells.

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^aDepartment of Neurology, Medical Faculty, Neuroregeneration Laboratory, Heinrich Heine University of Düsseldorf, D-40225 Düsseldorf, Germany; and ^bGeNeuro, CH-1228 Plan-les-Ouates, Switzerland

Author contributions: D.K., H.P., and P.K. analyzed data and wrote the paper.

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¹To whom correspondence may be addressed. Email: kuery@uni-duesseldorf.de.

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