

## Supplementary Information

**Table S1 Peripheral blood T cell frequencies**

|                     | CD3 <sup>+</sup>    | CD4 <sup>+</sup> CD3 <sup>+</sup> | CD8 <sup>+</sup> CD3 <sup>+</sup> | CD4:CD8 ratio      |
|---------------------|---------------------|-----------------------------------|-----------------------------------|--------------------|
| HC ( <i>n</i> = 56) | 70.88 (64.59–74.21) | 44.74 (38.96–50.97)               | 18.69 (16.05–23.56)               | 2.25 (1.75–3.14)   |
| MS ( <i>n</i> = 95) | 66.73 (58.36–72.38) | 45.29 (38.87–51.39)               | 15.57 (12.63–20.40)               | 2.94 (2.12–3.64)   |
| <i>P</i> value      | 0.006 <sup>a</sup>  | 0.845 <sup>b</sup>                | 0.001 <sup>b</sup>                | 0.006 <sup>a</sup> |

Median (interquartile range) percentages of T cells within PBMC. HC: healthy control subjects.

<sup>a</sup>Mann–Whitney rank sum test; <sup>b</sup>Student's *t* test. This data is derived from the results of our previous study on memory T cell subsets,<sup>13</sup> which included all of the subjects in the present study as well as additional ones.

**Table S2 Frequencies of memory T cell subsets**

|                             | CD4 <sup>+</sup>      |                      |                        |                      | CD8 <sup>+</sup>    |                     |                     |                     |                        |
|-----------------------------|-----------------------|----------------------|------------------------|----------------------|---------------------|---------------------|---------------------|---------------------|------------------------|
|                             | N                     | CM                   | EM                     | EMRA                 | N                   | CM                  | EM                  | EMRA                | EM/EMRA                |
| HC ( <i>n</i> = 56)         | 10.29<br>(7.16–16.54) | 8.99<br>(5.69–12.34) | 14.44<br>(11.30–19.76) | 7.29<br>(4.28–8.92)  | 3.99<br>(2.33–5.22) | 1.50<br>(0.99–2.17) | 6.76<br>(4.53–8.07) | 6.11<br>(4.66–9.36) | 13.00<br>(10.53–16.52) |
| MS ( <i>n</i> = 95)         | 9.63<br>(5.65–13.54)  | 7.45<br>(4.63–10.64) | 16.77<br>(11.4–22.94)  | 7.08<br>(4.55–11.69) | 2.88<br>(1.73–4.63) | 1.53<br>(0.84–2.23) | 5.31<br>(3.43–6.68) | 5.06<br>(3.43–7.34) | 10.60<br>(7.69–14.06)  |
| <i>P</i> value <sup>a</sup> | 0.130                 | 0.048                | 0.165                  | 0.443                | 0.083               | 0.870               | 0.002               | 0.015               | 0.001                  |

Median (interquartile range) percentages of memory T cell subsets within PBMC. N: naïve T cells; HC: healthy control subjects. <sup>a</sup>Mann–Whitney rank sum test. This data is derived from the results of our previous study on memory T cell subsets,<sup>13</sup> which included all of the subjects in the present study as well as additional ones.

## Defective T cell control of Epstein–Barr virus infection in multiple sclerosis

**Table S3 Frequencies of LCL-specific T cells in PBMC in EBV-seronegative and EBV-seropositive healthy subjects**

|                                   | CD3 <sup>+</sup>       | CD4 <sup>+</sup>       | CD8 <sup>+</sup>       | CD8 <sup>+</sup> N     | CD8 <sup>+</sup> CM    | CD8 <sup>+</sup> EM    | CD8 <sup>+</sup> EMRA  |
|-----------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| EBV-seronegative ( <i>n</i> = 6)  | 0.000<br>(0.000–0.001) | 0.000<br>(0.000–0.002) | 0.000<br>(0.000–0.001) | 0.000<br>(0.000–0.000) | 0.000<br>(0.000–0.000) | 0.001<br>(0.000–0.001) | 0.000<br>(0.000–0.000) |
| EBV-seropositive ( <i>n</i> = 56) | 0.283<br>(0.136–0.395) | 0.035<br>(0.016–0.073) | 0.183<br>(0.089–0.304) | 0.000<br>(0.0–0.001)   | 0.003<br>(0.002–0.008) | 0.152<br>(0.071–0.261) | 0.013<br>(0.004–0.056) |
| <i>P</i> value <sup>a</sup>       | < 0.0001               | < 0.0001               | < 0.0001               | 0.018                  | < 0.0001               | < 0.0001               | < 0.0001               |

Median (interquartile range) percentages of LCL-specific T cells within PBMC. N: naïve T cells. <sup>a</sup>Mann–Whitney rank sum test.

**Table S4 Immunomodulatory therapies received by MS patients prior to venesection**

|                             | Number of patients treated | Percentage of patients treated <sup>a</sup> | Median time between treatment cessation and venesection (years) |
|-----------------------------|----------------------------|---|---|
| Any <sup>b</sup>            | 20                         | 21.1  |   |
| Interferon-β                | 16                         | 16.8  | 3   |
| Glatiramer acetate          | 5                          | 5.3   | 5   |
| Methotrexate                | 3                          | 3.2   | 1   |
| Azathioprine                | 2                          | 2.1   | 7   |
| Natalizumab                 | 1                          | 1.1   | 1   |
| Sulphasalazine <sup>c</sup> | 1                          | 1.1   | 2   |

<sup>a</sup>Percentage of treated patients within the total group of 95 MS patients. <sup>b</sup>Some patients had been treated with more than one immunomodulatory therapy prior to venection. <sup>c</sup>For polyarthropathy.

**Table S5 HLA class I typing in healthy subjects and MS patients**

| HLA-A  | HC                 | MS                 | HLA-B  | HC                 | MS                 |
|--------|--------------------|--------------------|--------|--------------------|--------------------|
| Allele | n (%) <sup>a</sup> | n (%) <sup>a</sup> | Allele | n (%) <sup>a</sup> | n (%) <sup>a</sup> |
| A*01   | 19 (37.3)          | 19 (32.2)          | B*07   | 14 (28.0)          | 21 (35.6)          |
| A*02   | 29 (56.9)          | 21 (35.6)          | B*08   | 12 (24.0)          | 8 (13.6)           |
| A*03   | 9 (17.6)           | 17 (28.8)          | B*13   | 4 (8.0)            | 1 (1.7)            |
| A*11   | 4 (7.8)            | 7 (11.9)           | B*14   | 8 (16.0)           | 6 (10.2)           |
| A*23   | 2 (3.9)            | 2 (3.4)            | B*15   | 6 (12.0)           | 8 (13.6)           |
| A*24   | 4 (7.8)            | 13 (22.0)          | B*18   | 2 (4.0)            | 8 (13.6)           |
| A*25   | 3 (5.9)            | 5 (8.5)            | B*27   | 3 (6.0)            | 5 (8.5)            |
| A*26   | 0 (0.0)            | 1 (1.7)            | B*35   | 7 (14.0)           | 10 (16.9)          |
| A*28   | 2 (3.9)            | 0 (0.0)            | B*37   | 1 (2.0)            | 3 (5.1)            |
| A*29   | 5 (9.8)            | 8 (13.6)           | B*38   | 3 (6.0)            | 0 (0.0)            |
| A*30   | 2 (3.9)            | 3 (5.9)            | B*39   | 1 (2.0)            | 6 (10.2)           |
| A*31   | 3 (5.9)            | 3 (5.1)            | B*40   | 6 (12.0)           | 3 (5.1)            |
| A*32   | 5 (9.8)            | 4 (6.8)            | B*41   | 0 (0.0)            | 2 (3.4)            |
| A*33   | 0 (0.0)            | 4 (6.8)            | B*44   | 11 (22.0)          | 18 (30.5)          |
| A*34   | 0 (0.0)            | 1 (1.7)            | B*45   | 0 (0.0)            | 2 (3.4)            |
| A*36   | 0 (0.0)            | 1 (1.7)            | B*46   | 0 (0.0)            | 1 (1.7)            |
| A*43   | 0 (0.0)            | 0 (0.0)            | B*49   | 3 (6.0)            | 1 (1.7)            |
| A*66   | 0 (0.0)            | 0 (0.0)            | B*50   | 0 (0.0)            | 0 (0.0)            |
| A*68   | 4 (7.8)            | 4 (6.8)            | B*51   | 3 (6.0)            | 4 (6.8)            |
| A*69   | 0 (0.0)            | 0 (0.0)            | B*52   | 0 (0.0)            | 1 (1.7)            |
| A*74   | 0 (0.0)            | 0 (0.0)            | B*53   | 0 (0.0)            | 0 (0.0)            |
| A*92   | 0 (0.0)            | 0 (0.0)            | B*55   | 2 (4.0)            | 2 (3.4)            |
|        |                    |                    | B*56   | 1 (2.0)            | 1 (1.7)            |
|        |                    |                    | B*57   | 3 (6.0)            | 3 (5.1)            |
|        |                    |                    | B*58   | 1 (2.0)            | 0 (0.0)            |
|        |                    |                    | B*59   | 0 (0.0)            | 0 (0.0)            |
|        |                    |                    | B*60   | 1 (2.0)            | 0 (0.0)            |
|        |                    |                    | B*62   | 1 (2.0)            | 0 (0.0)            |
|        |                    |                    | B*78   | 0 (0.0)            | 0 (0.0)            |

HLA-A and HLA-B typing results in 50 healthy control subjects (HC) and 59 MS patients. <sup>a</sup>Number (%) of subjects carrying each allele, either heterozygously or homozygously.