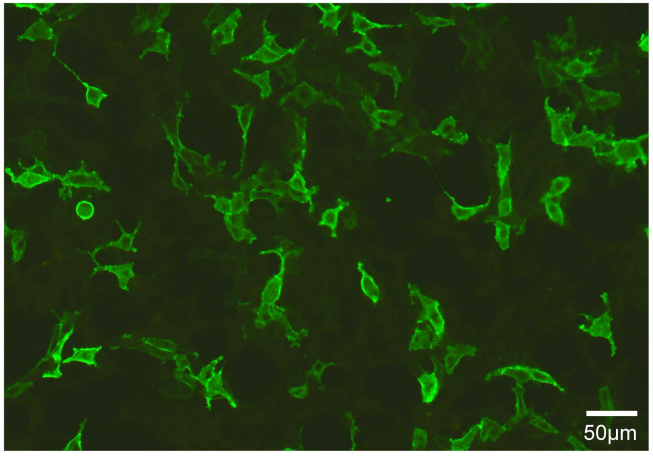
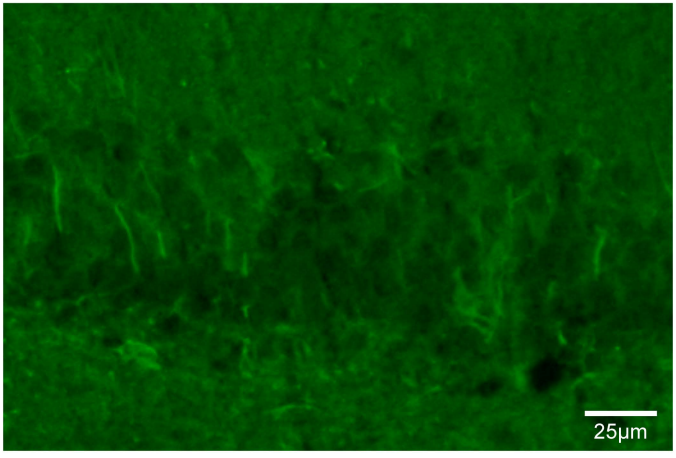
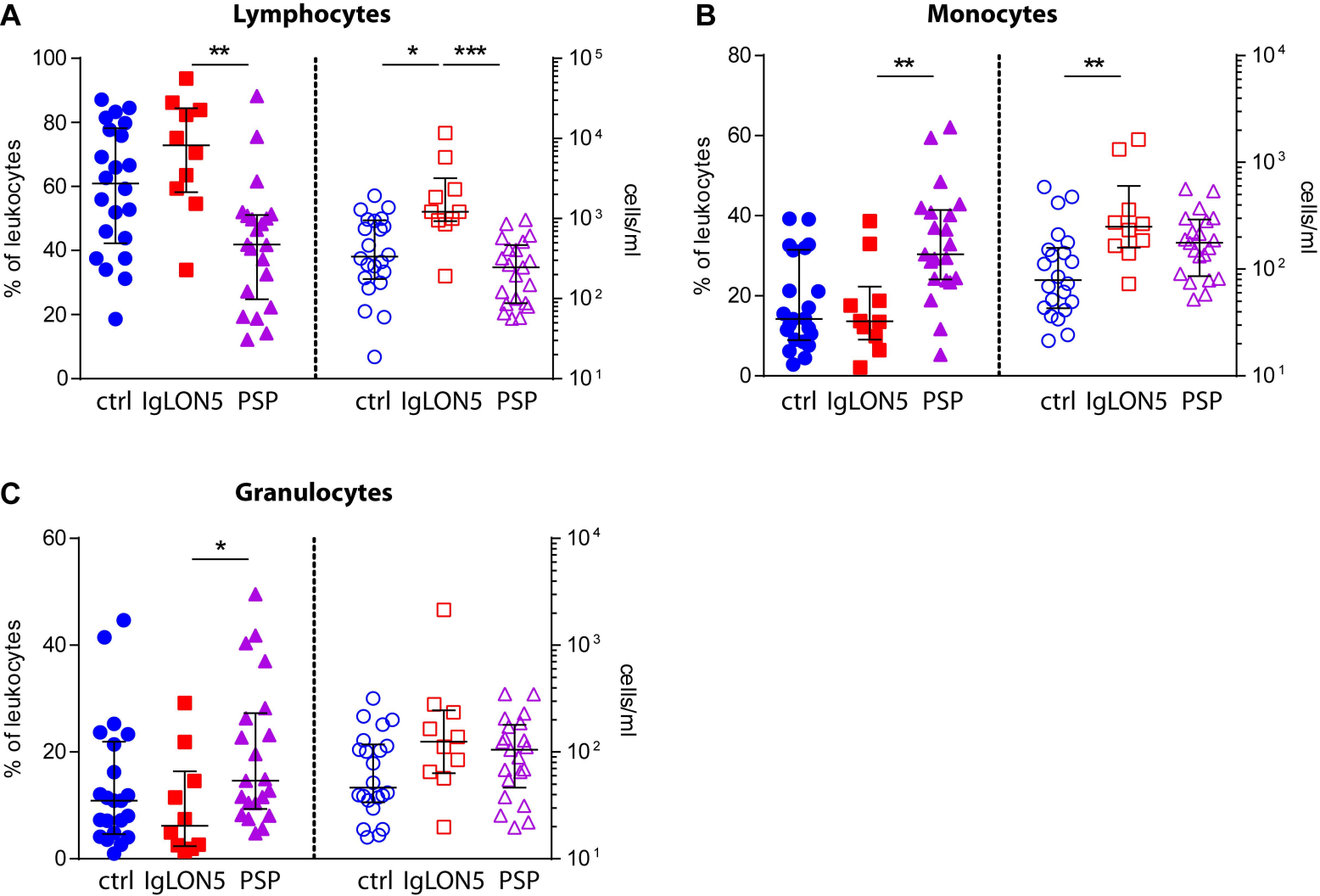
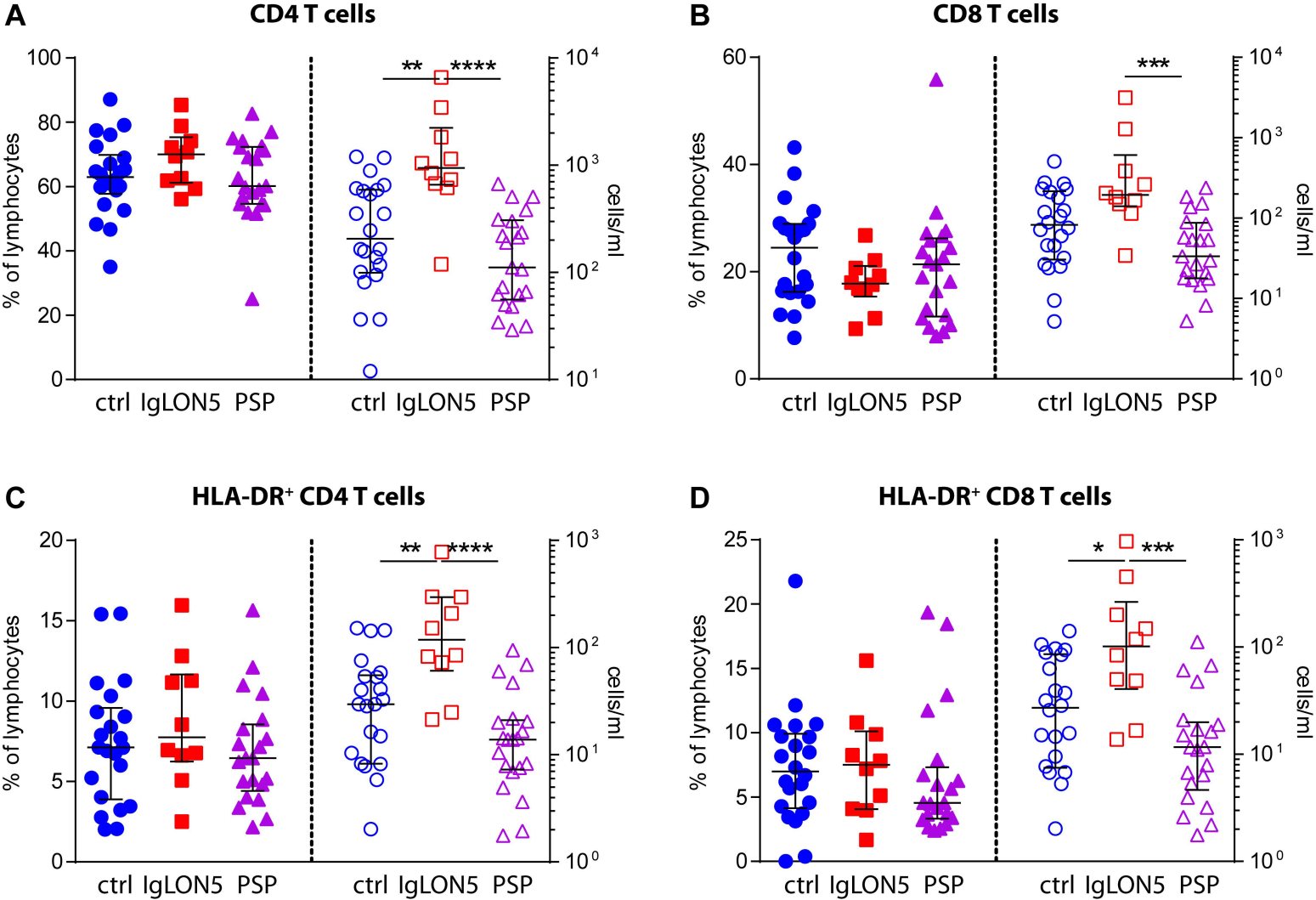
A

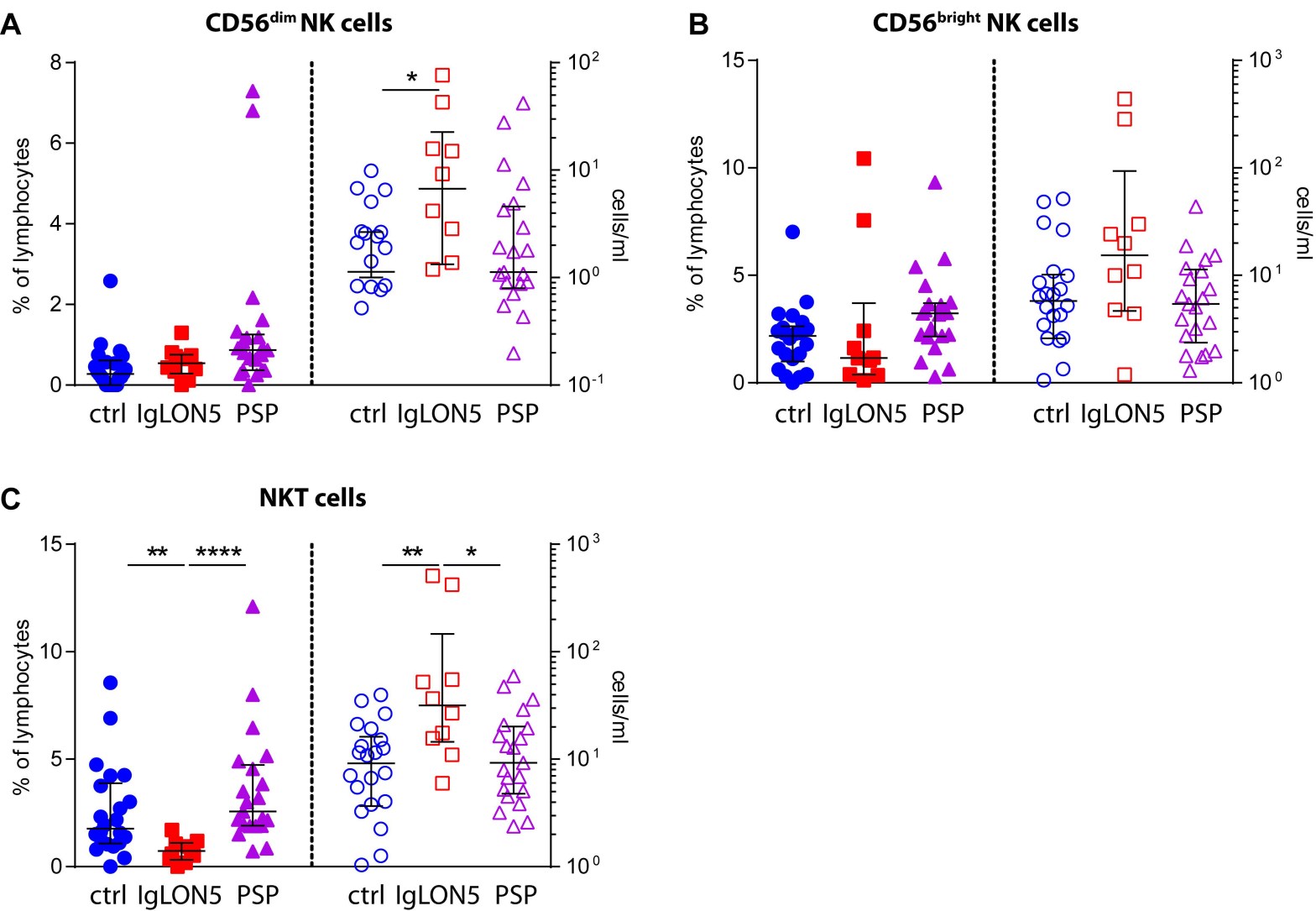


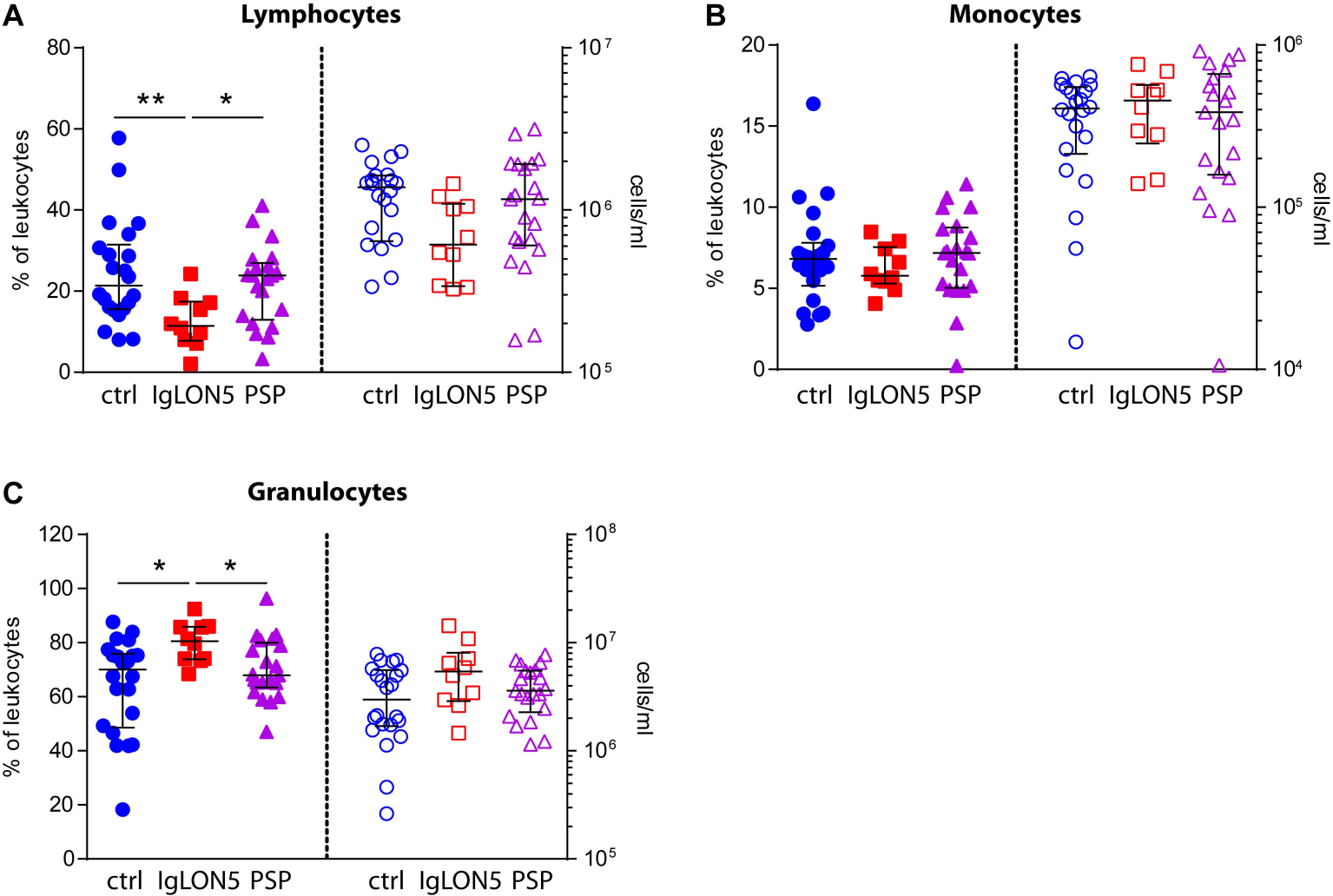
B

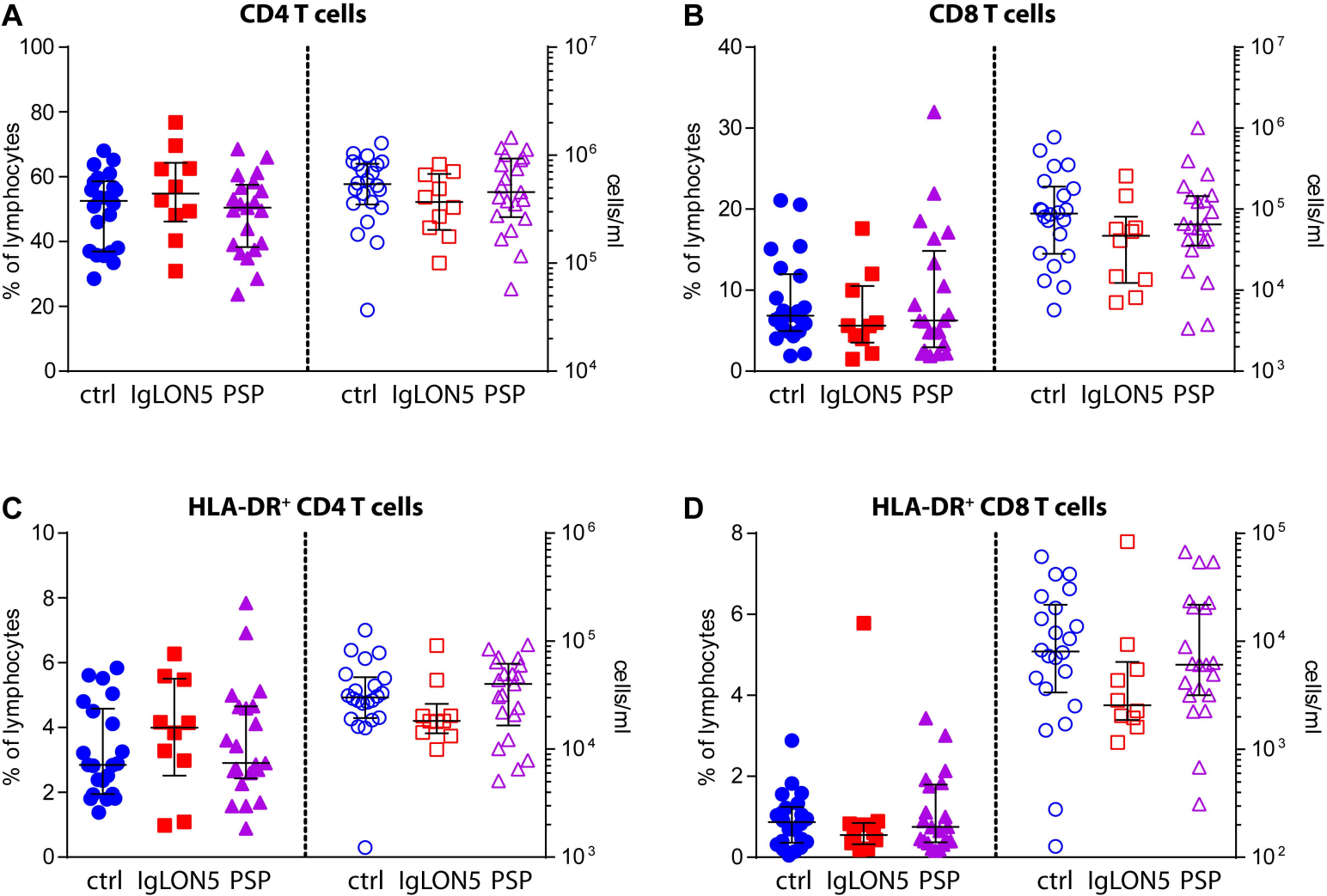



A
Lymphocytes
% of leukocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
B
Monocytes
% of leukocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
C
Granulocytes
% of leukocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP


A
CD4 T cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
**
****
B
CD8 T cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
***
C
HLA-DR+ CD4 T cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
**
****
D
HLA-DR+ CD8 T cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
*
***


A
CD56dim NK cells
% of lymphocytes
cells/ml
*
ctrl IgLON5 PSP
ctrl IgLON5 PSP
B
CD56bright NK cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
C
NKT cells
** ****
** *
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP


A
Lymphocytes
% of leukocytes
cells/ml
**
*
ctrl
IgLON5
PSP
ctrl
IgLON5
PSP
B
Monocytes
% of leukocytes
cells/ml
ctrl
IgLON5
PSP
ctrl
IgLON5
PSP
C
Granulocytes
% of leukocytes
cells/ml
*
*
ctrl
IgLON5
PSP
ctrl
IgLON5
PSP


A
CD4 T cells
% of lymphocytes
cells/ml
ctrl
IgLON5
PSP
B
CD8 T cells
C
HLA-DR+ CD4 T cells
D
HLA-DR+ CD8 T cells

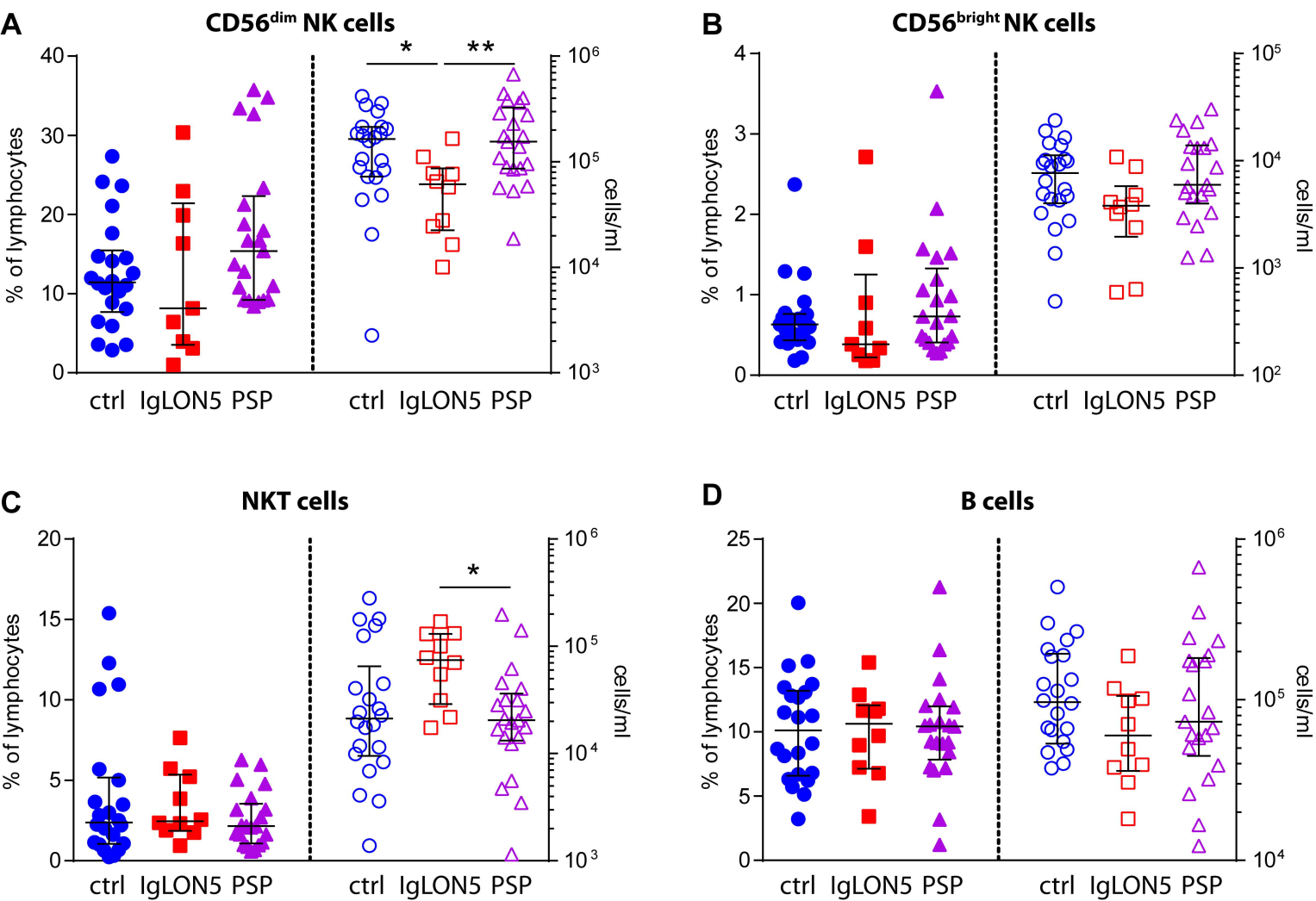

A
CD56dim NK cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
*
**
B
CD56bright NK cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
C
NKT cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP
*
D
B cells
% of lymphocytes
cells/ml
ctrl IgLON5 PSP
ctrl IgLON5 PSP

Figure Legends

Figure 1: CSF findings in Anti-IgLON5 disease.
(A) Cell count in CSF samples obtained from 22 controls without any sign of inflammatory CNS disorders (blue circles), 10 IgLON5 patients (red squares) and 20 PSP patients (violet triangles) as determined by Fuchs-Rosenthal chamber. (B) Representative dot plot from flow-cytometric analysis of CSF used to quantify $CD19^{high}CD138^{neg}$ B cells and $CD19^{low}CD138^{high}$ plasma cells. (C, D) Relative (left, closed symbols) and total (right, open symbols) levels of B cells (C) and plasma cells (D) in the CSF. Error bars indicate the median and interquartile range. Statistical analysis was done by Kruskal-Wallis test with Dunn's post-test, *p<0.05. **p<0.01, ***p<0.001, ****p<0.0001.

Supplementary Figure 1:
(A) IgLON5 fluorescence of transfected HEK cells (cell based assay). (B) Fine-granular IgLON5 fluorescence of the hippocampal molecular layer in rodent brain slices (histological assay).

Supplementary Figure 2:
Relative (left, closed symbols) and total (right, open symbols) levels of Lymphocytes (A), Monocytes (B), and Granulocytes (C) determined by flow cytometry in CSF samples obtained from 22 controls without any sign of inflammatory CNS disorders (blue circles), 10 IgLON5 patients (red squares) and 20 PSP patients (violet triangles). Error bars indicate the median and interquartile range. Statistical analysis was done by Kruskal-Wallis test with Dunn's post-test, *p<0.05. **p<0.01, ***p<0.001, ****p<0.0001.

Supplementary Figure 3:
Relative (left, closed symbols) and total (right, open symbols) levels of CD4 T cells (A), CD8 T cells (B), $HLA\text{-}DR^+$ CD4 T cells (C), and $HLA\text{-}DR^+$ CD8 T cells (D) determined by flow cytometry in CSF samples obtained from 22 controls without any sign of inflammatory CNS disorders (blue circles), 10 IgLON5 patients (red squares) and 20 PSP patients (violet triangles). Error bars indicate the median and interquartile range. Statistical analysis was done by Kruskal-Wallis test with Dunn's post-test, *p<0.05. **p<0.01, ***p<0.001, ****p<0.0001.

Supplementary Figure 4:
Relative (left, closed symbols) and total (right, open symbols) levels of $CD56^{dim}CD16^+$ NK cells (A), $CD56^{bright}CD16^{dim/-}$ NK cells (B), and NKT cells (C) determined by flow cytometry in CSF samples obtained from 22 controls without any sign of inflammatory CNS disorders (blue circles), 10 IgLON5 patients (red squares) and 20 PSP patients (violet triangles). Error bars indicate the median and interquartile range. Statistical analysis was done by Kruskal-Wallis test with Dunn's post-test, *p<0.05. **p<0.01, ***p<0.001, ****p<0.0001.

Supplementary Figure 5:
Relative (left, closed symbols) and total (right, open symbols) levels of Lymphocytes (A), Monocytes (B), and Granulocytes (C) determined by flow cytometry in blood samples obtained from 22 controls without any sign of inflammatory CNS disorders (blue circles), 10 IgLON5 patients (red squares) and 20 PSP patients (violet triangles). Error bars indicate the median and interquartile range. Statistical analysis was done by Kruskal-Wallis test with Dunn's post-test, *p<0.05. **p<0.01, ***p<0.001, ****p<0.0001.

Supplementary Figure 6:
Relative (left, closed symbols) and total (right, open symbols) levels of CD4 T cells (A), CD8 T cells (B), $HLA\text{-}DR^+$ CD4 T cells (C), and $HLA\text{-}DR^+$ CD8 T cells (D) determined by flow cytometry

in blood samples obtained from 22 controls without any sign of inflammatory CNS disorders (blue circles), 10 IgLON5 patients (red squares) and 20 PSP patients (violet triangles). Error bars indicate the median and interquartile range. Statistical analysis was done by Kruskal-Wallis test with Dunn's post-test, *p<0.05. **p<0.01, ***p<0.001, ****p<0.0001.

Supplementary Figure 7:
Relative (left, closed symbols) and total (right, open symbols) levels of $CD56^{dim}CD16^{+}$ NK cells (A), $CD56^{bright}CD16^{dim/-}$ NK cells (B), NKT cells (C), and B cells (D) determined by flow cytometry in blood samples obtained from 22 controls without any sign of inflammatory CNS disorders (blue circles), 10 IgLON5 patients (red squares) and 20 PSP patients (violet triangles). Error bars indicate the median and interquartile range. Statistical analysis was done by Kruskal-Wallis test with Dunn's post-test, *p<0.05. **p<0.01, ***p<0.001, ****p<0.0001.

	n	IgLON5 Mean (Min-Max)	n	PSP Mean (Min-Max)	Significance (p-value, unpaired t-test)
Age at presentation, years	11	65.8 (49-81)	20	71,0 (59-84)	0.027
Age at onset, years	11	61.5 (46-74)	20	68.4 (58-82)	0.107
Duration of disease at CSF investigation, years	10	4.0 (1-9)	20	2.7 (1-7)	0.216
mRS at presentation	11	1,9 (1-3)	20	1,7 (1-3)	0.498
Atrophy in MRI at presentation (specific midbrain atrophy)	11	5 (0)	20	13 (7)	0.429
CSF-ß-Amyloid$_{1-42}$ (pg/ml)	5	965 (589-1320)	16	1134 (430-1843)	0.435
CSF-hTau (pg/ml)	5	206 (67-364)	16	334 (13-966)	0.259

eTable 1: Comparison of clinical, MRI and neurodegeneration markers in CSF in patients with anti-Iglon5 disease and PSP

Supplementary Methods

For flow-cytometric analysis, cells from the CSF and EDTA-blood samples were analyzed in parallel. CSF was spun down at 290g for 15min and the supernatant was removed. CSF cells were re-suspended in parallel to 100µl EDTA-blood in 1ml VersaLyse (Beckman Coulter) and incubated for 10 min at room temperature. Afterwards, cells were washed twice with flow cytometry buffer (FC buffer: PBS, 2% heat-inactivated FCS, 2mM EDTA; 300g 4min) and stained in 100µl FC buffer supplemented with fluorochrome-conjugated antibodies directed against CD3 (UCHT1), CD4 (13B8.2), CD8 (B9.11), CD14 (RM052), CD16 (3G8), CD19 (J3-119), CD45 (J33), CD56 (N901), CD138 (B-A38), and HLA-DR (Immu-357) (all Beckman Coulter, clones in brackets) for 30min. Finally, cells were washed, re-suspended in FC buffer + 20µl flow count fluorospheres (Beckman Coulter), and acquired using a Navios flow cytometer (Beckman Coulter). Resulting files were analyzed using Kaluza 2.1 software (Beckman Coulter). CSF ß-Amyloid$_{1-42}$ and hTau were analyzed by ELISA microplate reader ELX 808 (BIO-TEK) using kits from Fujirebio and IBL, respectively, following the manufactures instructions.