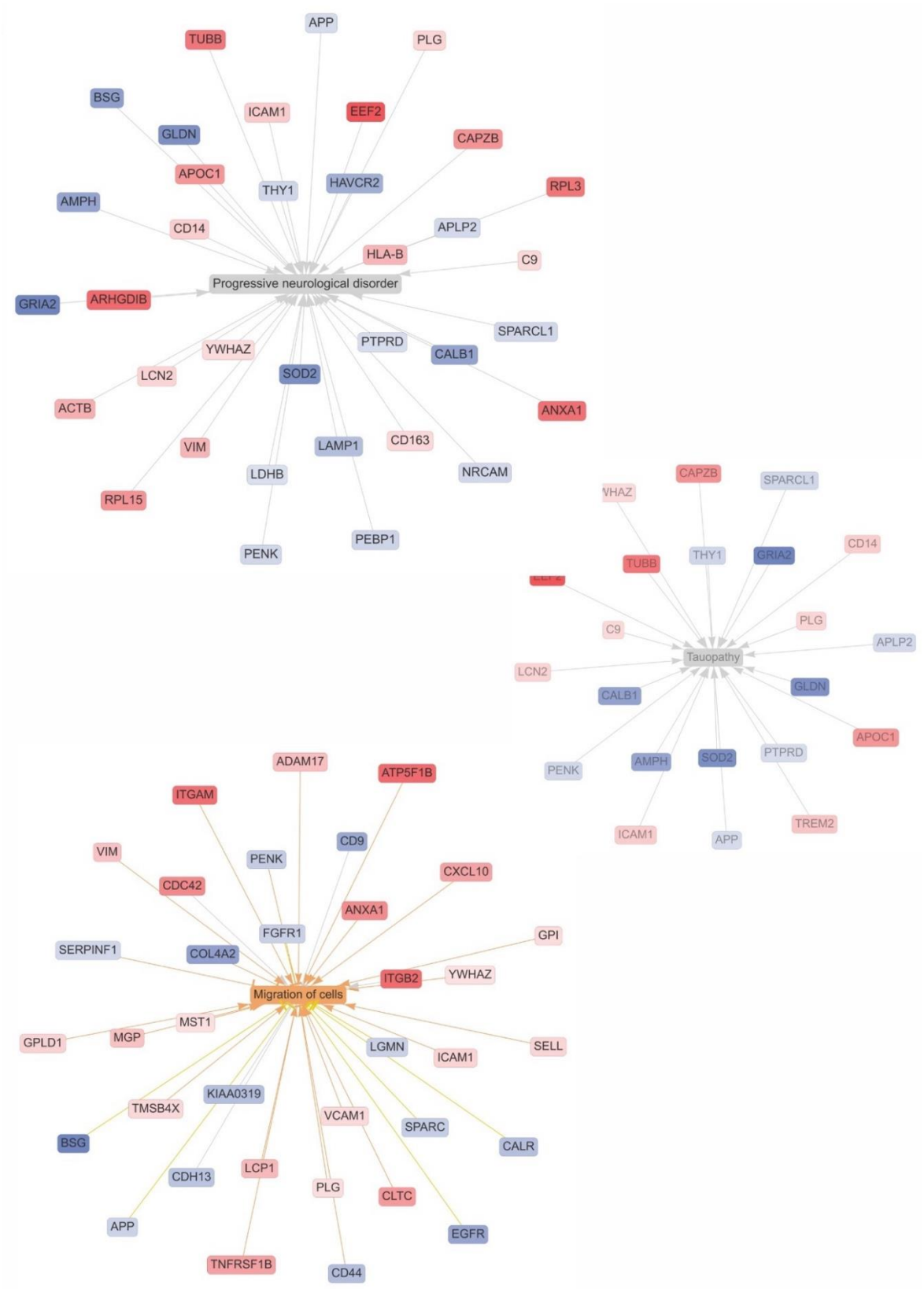
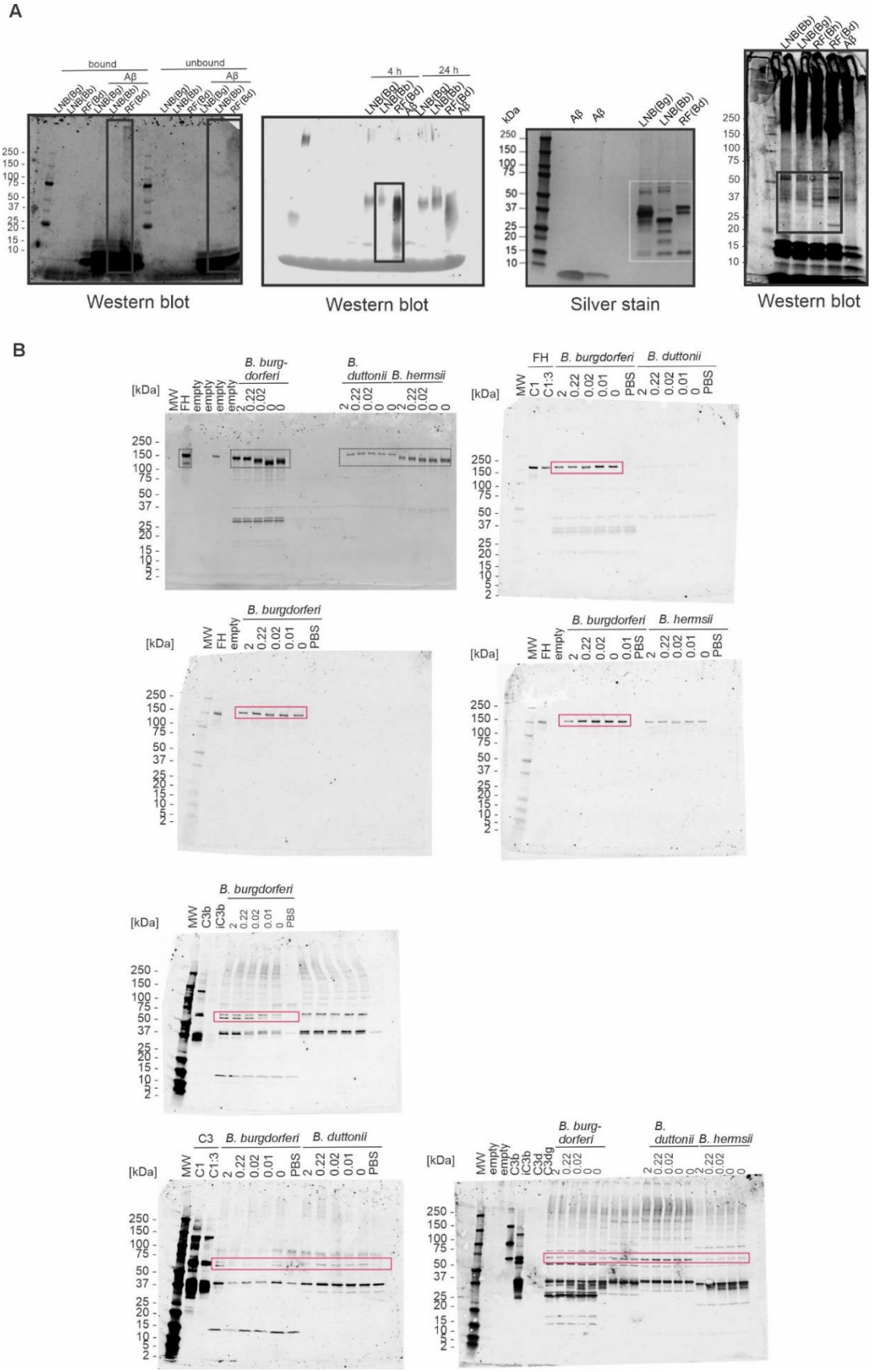
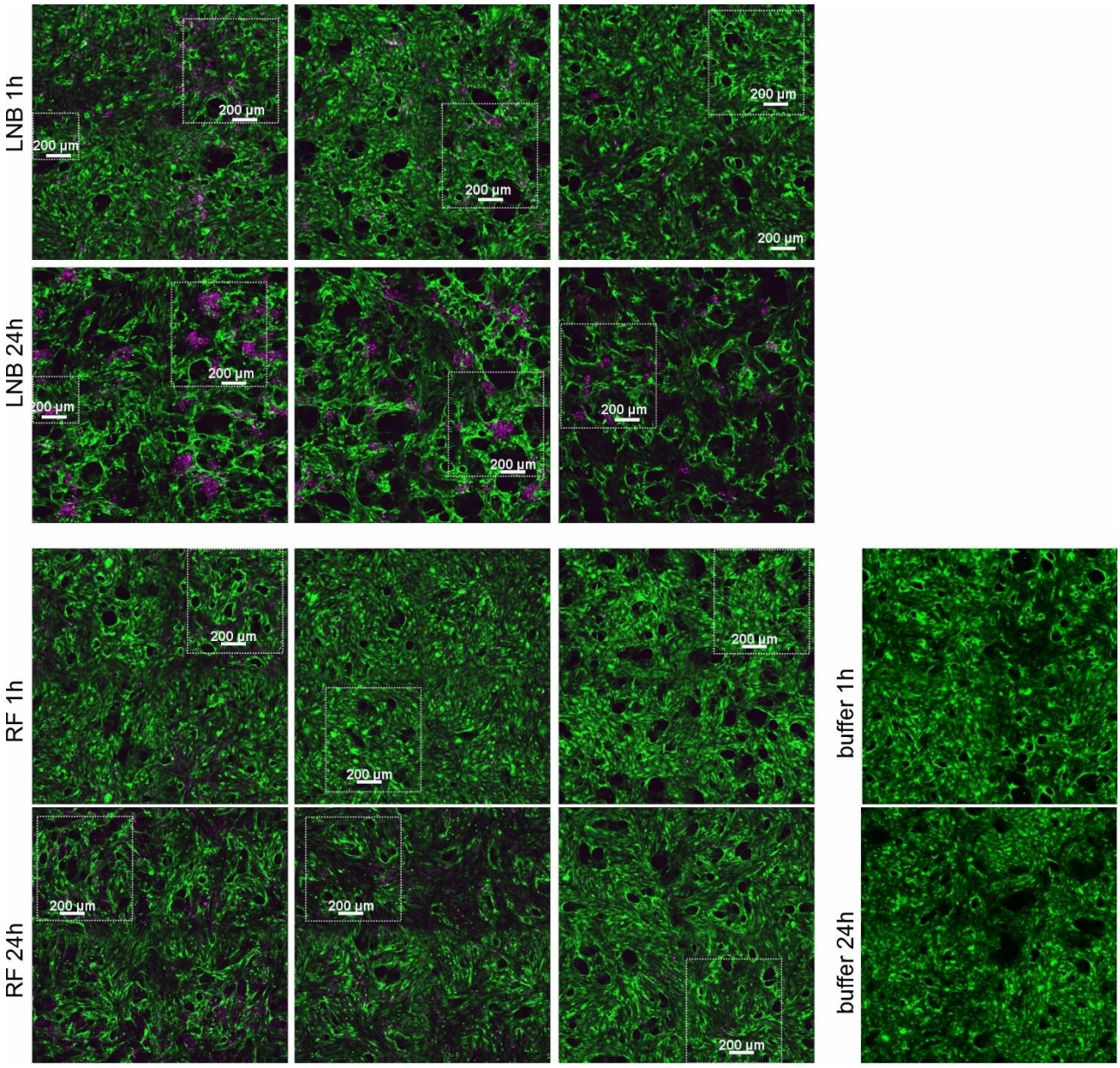
Supplementary information



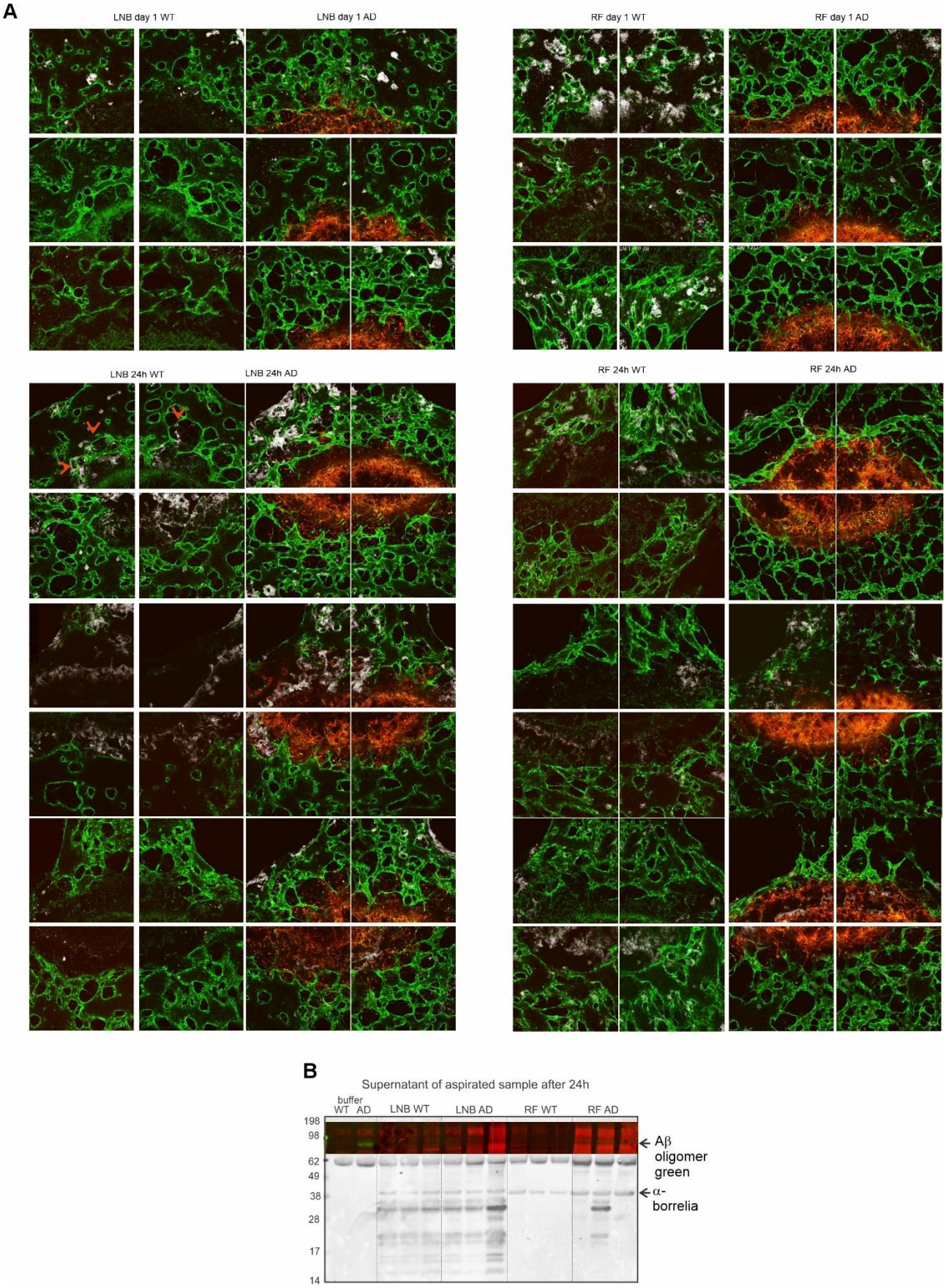
Extended data Fig. S1. Mass spectrometry analysis of LNB CSF proteome identifies proteins from pathways that are significantly affected in LNB.



Extended data Fig. S2. SDS-PAGE and Western blots of *Borrelia* spp. bacteria and surface proteins. A, Aβ binding to *Borrelia* spp. bacteria and surface proteins including a silver stain showing the isolated surface proteins. **B.** A silver stain of a Western blot showing FH and C3b/iC3b deposition on *Borrelia* spp.



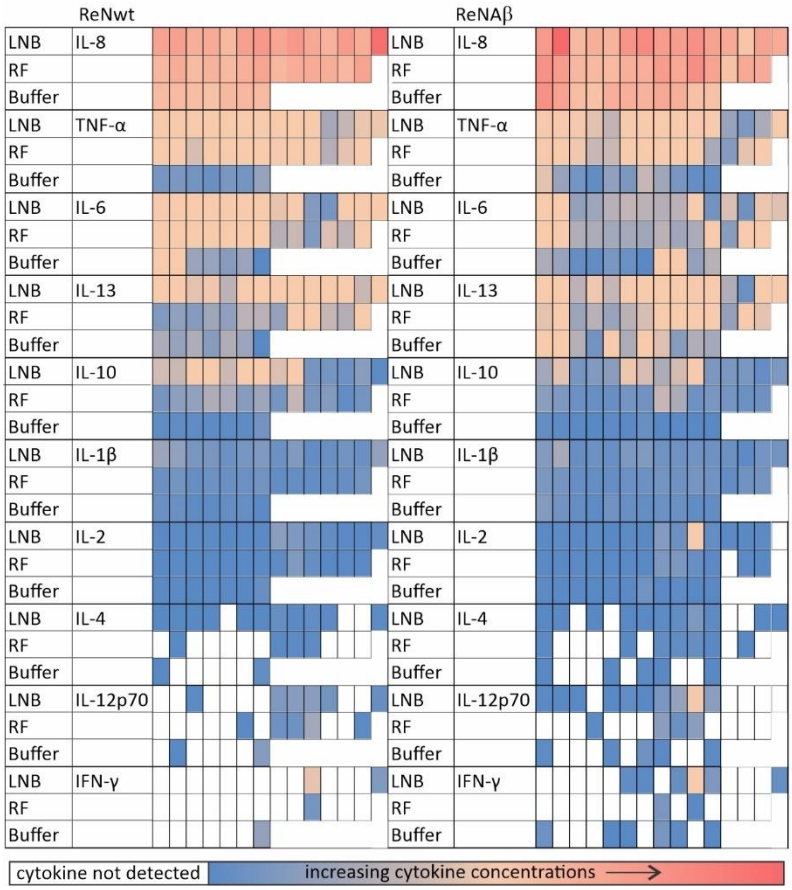
Extended data Fig. S3. *Borrelia* spp. invasion in a vascular (perfusable) BBB model. LNB *B. burgdorferi* and RF *B. hermsii* infections shown in the same device at 1h and 24h time points. The regions of interests shown in Fig. 4 are indicated by a square in the images.



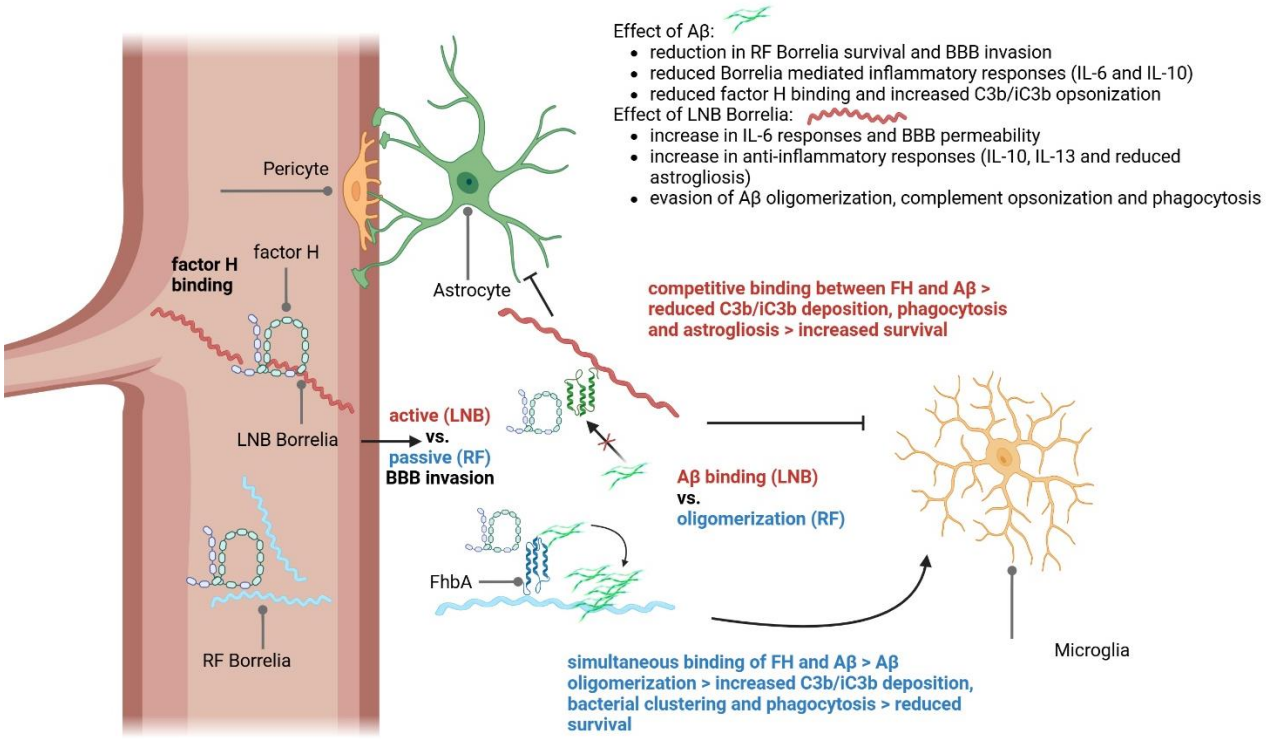
Extended data Fig. S4. *Borrelia* spp. invasion in a 3D neurovascular (perfusable BBB vascular model combined with 3D triculture) model. A, Infection of 3DBBB showing BBB invasion of

Borrelia spp. in the wild type (WT) culture (no Aβ over expression) vs. AD culture (Aβ over expression) at 1 h and 24h time points on the same device. **B,** WB of the aspirate analyzed by anti-borrelia antibody for the presence of bacteria that were not attached to the vascular wall within 24h. The presence of Aβ oligomer can be detected on the AD culture incubated with buffer suggesting that the bacteria bind Aβ from the supernatant.

		microglia independent	anti-inflammatory microglia dependent		inflammatory microglia dependent			no role in Ab defence or infection in the tetraculture			
3D triculture		IL-6	IL-10	IL-13	IL-1β	IL-8	TNF-α	IL-12p70	IL-2	IL-4	IFN-γ
no iMGL	Bb(LNB)	1.19294949	0.007723485	0	0	2.264412643	0	0	0	0	0
	Bh(RF)	0.881146553	0.006633145	0	0	1.963946205	0	0	0	0	0
	Buff	0.846915738	0.003711212	0	0	2.110662395	0	0	0	0	0
	Bb(LNB)	1.987832378	0.005784539	0	0	3.921459209	0	0	0	0	0
	Bh(RF)	1.506509839	0.003891446	0	0	1.542792527	0	0	0	0	0
	Buff	2.33691643	0.008792048	0	0	2.850885947	0	0	0	0	0
3D tetraculture		IL-6	IL-10	IL-13	IL-1β	IL-8	TNF-α	IL-12p70	IL-2	IL-4	IFN-γ
iMGL	Bb(LNB)	4.032894931	2.000072866	2.215668032	0.429062994	246.9672361	5.177221893	0	0.0505035	0	0
	Bh(RF)	3.562766194	0.64991047	0.984554479	0.230156706	167.1180519	3.175144118	0	0.0266597	0	0
	Buff	1.527237462	0.109535018	1.0655239	0.177121684	125.9618129	0.442320021	0	0.0247666	0	0
	Bb(LNB)	1.892332171	1.030833587	2.486918703	0.347701921	264.0385547	5.198658028	0	0.0836801	0	0
	Bh(RF)	1.732367491	0.344822894	1.533020727	0.235952611	200.0206474	3.207237859	0	0.0338089	0	0
	Buff	0.82335321	0.04524	1.598579657	0.248357392	191.775979	0.655470457	0	0.0320227	0	0



Extended data Fig. S5. Cytokine levels of *Borrelia* spp. infected 3D cultures. (above) Comparison of cytokine levels in pg/ml between 3D tri- and tetracultures. (below). Heat map of relative cytokine levels in 3D tetraculture.



Extended data Fig. S6. Schematic representation of Aβ/complement response to *Borrelia* spp. infection. While LNB *Borrelia* spp. show clustering on the vascular surface and active BBB invasion Aβ reduces attachment RF Borrelia bacteria at this stage. Passive invasion of RF *Borrelia* spp. through BBB is enabled by the exacerbated immune response. In the neuronal site (the brain) strong binding of FH, evasion of Aβ olgomerization and triggering of specific immune responses (IL-10, IL-13) leads to evasion of complement and glial cells which favor persistence of LNB *Borrelia* spp. infection. On the contrary, the action of Aβ on RF *Borrelia* spp. leads to microbial clustering and phagocytosis by microglia.