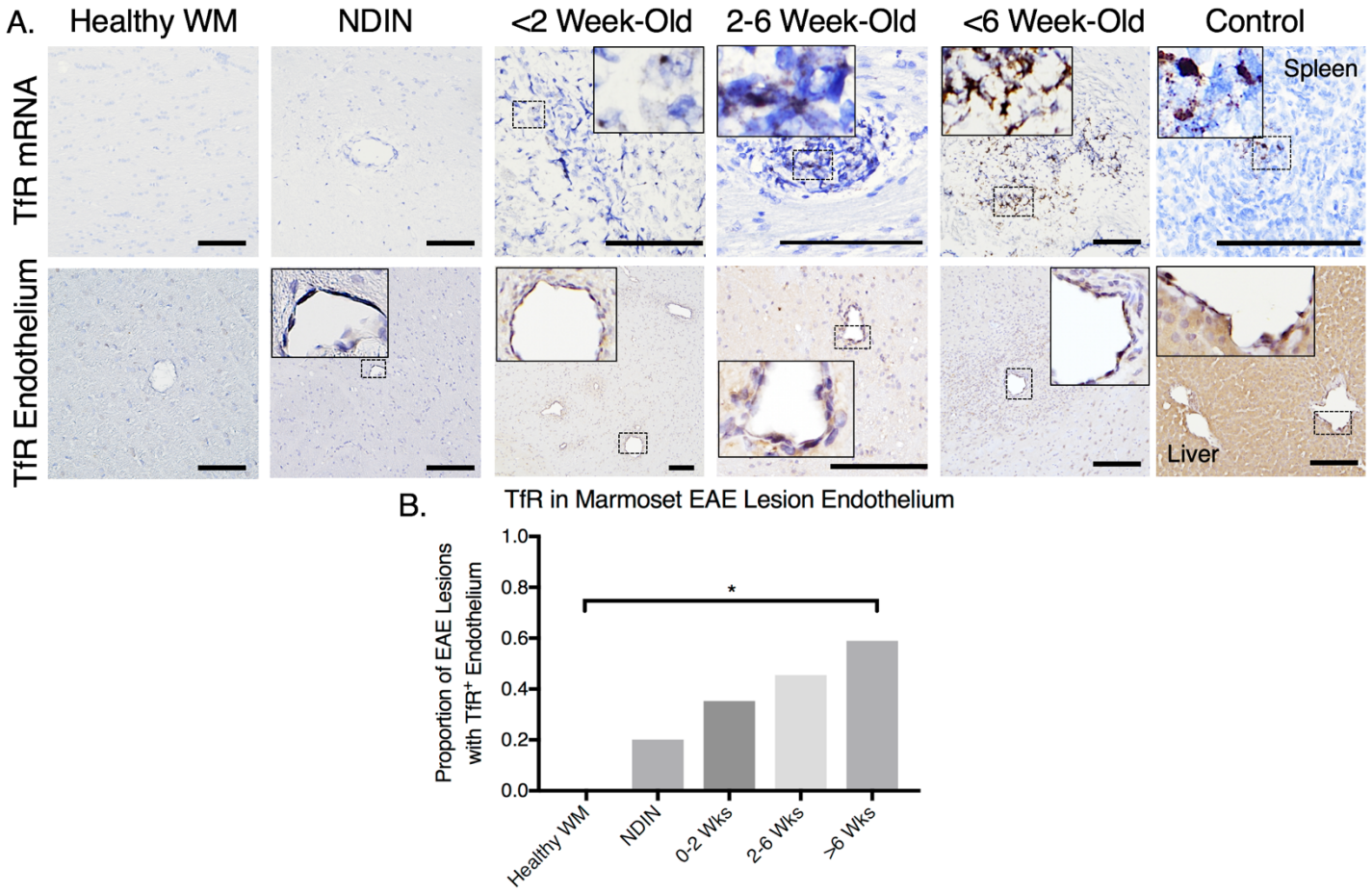
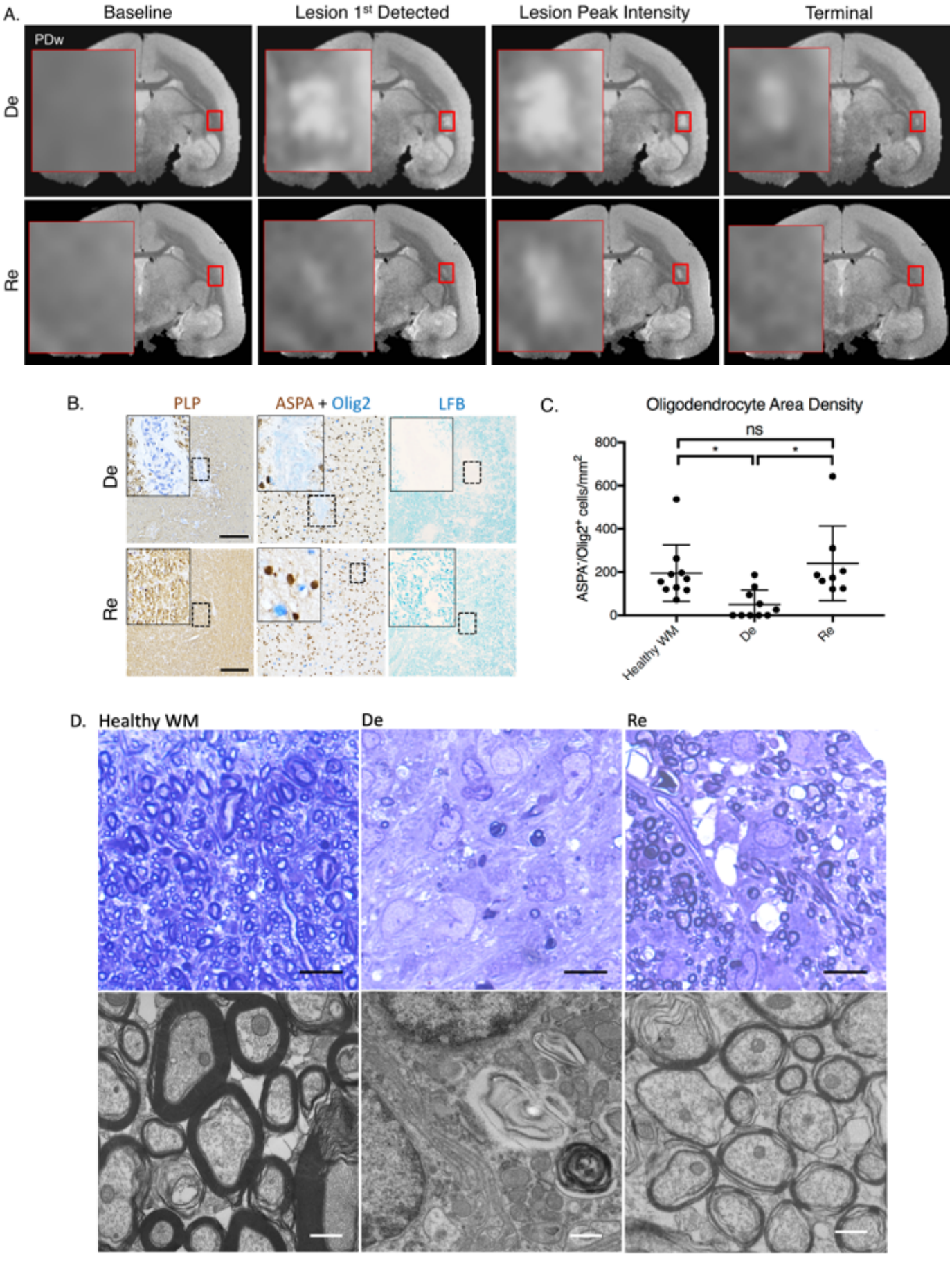
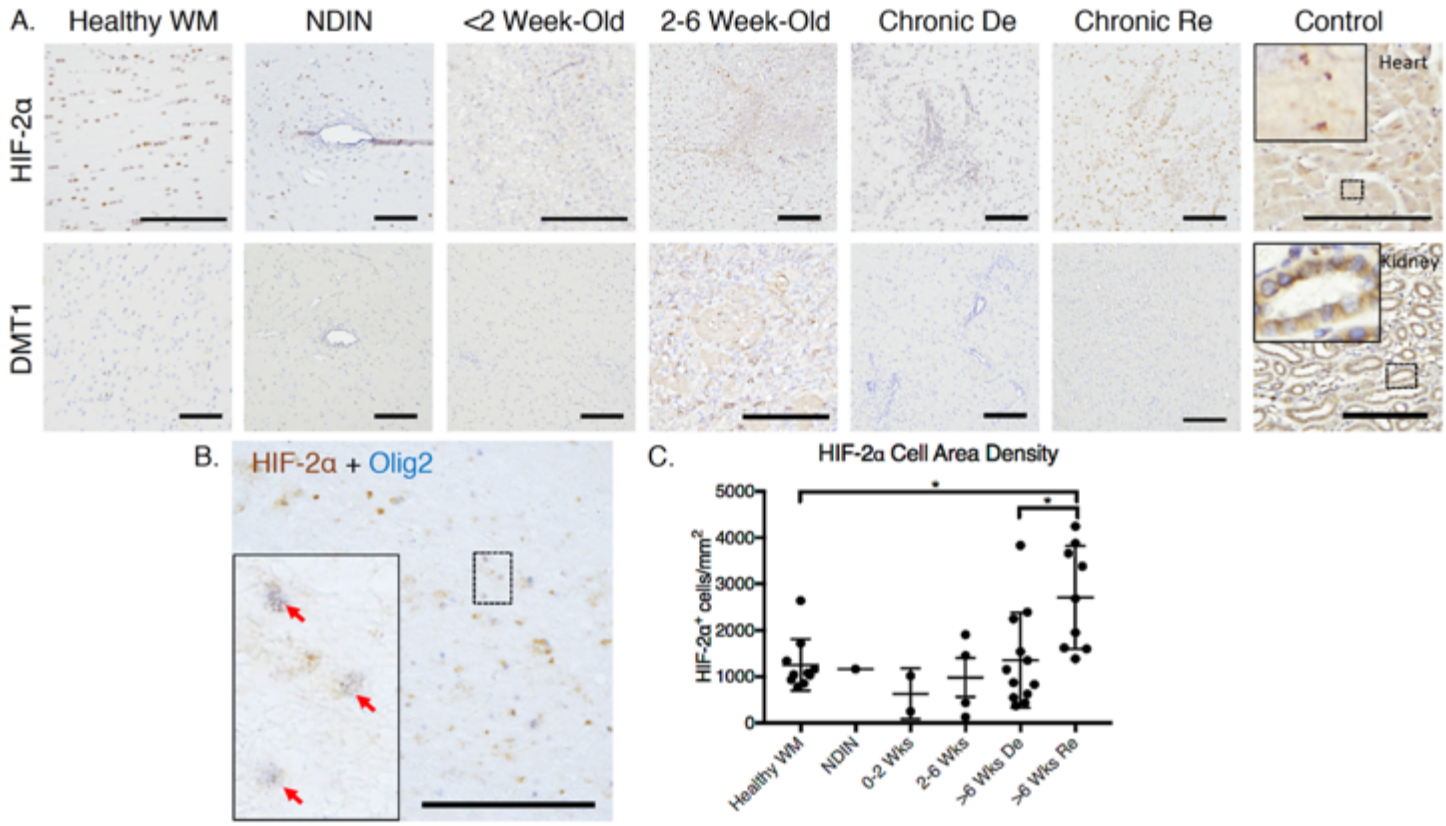


Supplementary Figure 1. Endothelial cells express transferrin receptor in marmoset EAE lesions. (A) Transferrin receptor (TfR) mRNA is detected in <2-week-old, 2–6-week-old, and >6-week-old lesions, but not in healthy white matter or non-demyelinated inflammatory nodules (NDIN). TfR is detected in the endothelium of all EAE lesions. (B) Quantification of the prevalence of EAE lesions with increased TfR expression in the endothelium shows that TfR increases as lesions age and is highest in >6-week-old, demyelinated lesions. Positive controls = marmoset spleen and liver. Scale bar = 100µm. Counterstain = hematoxylin. Lesions selected from marmosets #1, 4, 6, 8, 9, 10, and 11. *$p < 0.05$ (Dunn's multiple comparisons test).


A.
Baseline
Lesion 1st Detected
Lesion Peak Intensity
Terminal
PDw
De
Re
B.
PLP
ASPA + Olig2
LFB
De
Re
C.
Oligodendrocyte Area Density
ns
*
*
ASPA+/Olig2+ cells/mm2
800
600
400
200
0
Healthy WM
De
Re
D.
Healthy WM
De
Re

Supplementary Figure 2. Marmoset EAE lesion repair is detectable by serial in vivo MRI and histopathology, confirmed by transmission electron microscopy. (A) Serial in vivo proton density-weighted (PDw) MRI, in combination with histopathology, was used to identify both demyelinated (De) and remyelinated (Re) EAE lesions, in which the latter demonstrated hyperintense signal that returned to isointensity by the terminal time point. (B) Immunohistochemical staining for representative demyelinated (De) and remyelinated (Re) chronic (>6-week-old) EAE lesions, identical to the lesions shown in panel A, shows that remyelinated lesions have abundant myelin (PLP and especially LFB) and oligodendrocyte-lineage cells (ASPA + Olig2) in the lesion area, whereas demyelinated lesions do not. (C) Quantification of $ASPA^{-}/Olig2^{+}$ oligodendrocyte-lineage cells in demyelinated vs. remyelinated lesions shows that remyelinated lesions have significantly more oligodendrocytes, indistinguishable from the level in healthy white matter. (D) Transmission electron microscopy (TEM) image of control white matter, demyelinated lesion, and remyelinated lesion. Top panel shows toluidine blue staining, and the bottom row demonstrates EM images. Compared to the control panel, the putative demyelinated lesion has minimal myelin sheaths, whereas the putative remyelinated lesion has apparently thin myelin, as expected for remyelination. Black scale bars = 10μm; white scale bars = 500nm. *$p < 0.05$ (ANOVA). Scale bar = 100μm. Counterstain = hematoxylin for PLP. Lesions selected from marmosets #1, 2, 5, and 10.



Supplementary Figure 3. **Spatiotemporal dynamics of HIF-2α levels in marmoset EAE lesions does not correlate with that of DMT1.** (A) HIF-2α is found in healthy white matter and at all stages of EAE lesion development, but not in clear correlation with DMT1 levels. (B) HIF-2α is present in Olig2^{+} oligodendrocyte-lineage cells (red arrows). (C) Graphical representation of the prevalence of HIF-2α^{+} cells in marmoset EAE lesions, showing increased levels in remyelinated lesions. Positive control = marmoset heart for HIF-2α; DMT1 is reproduced from Figure 2. Scale bar = 100μm. Counterstain = hematoxylin for (A). *$p < 0.05$ (one-way ANOVA). Lesions selected from marmosets #1, 3, 6, 7, 9, and 10.

	Sex	Age at Baseline	Experimental Duration (months)	Additional Inoculation	Lesion Location
Marmoset #1	M	5.5	14	N/A	Frontal, temporal, and occipital lobe
Marmoset #2	M	5.5	14	N/A	Temporal lobe
Marmoset #3	F	3	3.5	N/A	Temporal and occipital lobes
Marmoset #4	F	3	4	N/A	Internal capsule; frontal, temporal, and occipital lobes
Marmoset #5	M	2.5	13	N/A	Temporal and occipital lobes
Marmoset #6	M	2.5	9.5	N/A	Optic nerve, parietal and occipital lobes
Marmoset #7	F	2.5	1	HHV6B	Frontal lobe
Marmoset #8	F	3.9	2.5	HHV6B	Parietal lobe
Marmoset #9	F	4.6	1	N/A	Optic nerve, frontal and parietal lobes
Marmoset #10	M	3.6	4.5	N/A	Parietal, temporal, and occipital lobes
Marmoset #11	F	2.5	3	HHV6A	Frontal lobe
Marmoset #12	F	4.6	5	N/A	Frontal, parietal, and temporal lobes
Marmoset #13	F	4.3	2	HHV6A	Parietal lobe

Supplementary Table 1. Demographics of marmosets involved in the study. Data from 13 marmosets (5 male and 8 female) ages 2–6 years old at baseline, were included in the study. Additional inoculation, experimental durations, and lesion locations are also listed. HHV = human herpes virus.

	MR Sequence	In-plane res. (µm)	ST (µm)	TE (ms)	TR (ms)	FA	NA	TAT (min)
Marmosets #1–6 In vivo	PD-weighted	150 x 150	1000	16	2300	90	1	7.7
	T2*-weighted	150 x 150	1000	18	2150	70	1	9.2
Marmosets #7–13 In vivo	PD-weighted	125 x 125	600	16	2300	90	2	22
	T2*-weighted	125 x 125	600	22	2132	70	2	20
Marmosets Ex vivo	T2*-weighted	100 x 100	100	10	50	16	10	36 (hours)
Human In vivo	T2*-weighted	215 x 215	1000	32	6000	50	1	8.5
Human Ex vivo	T2*-weighted	420 x 420	420	26	60	10	4	135

Supplementary Table 2. Compilation of proton density (PD) and T2*-weighted (*in-vivo* and *ex-vivo*) MRI sequence parameters used for marmoset and human brain tissue. ST = slice thickness; TE = echo time; TR = repetition time; FA = flip angle; NA = number of averages; TAT = total acquisition time.

	Sex	Age	Disease Duration (Years)	EDSS	RRMS	PPMS	SPMS	Treatment
In vivo	M = 11; F = 28	53.3 ± 13.0	17 ± 11.3	3 (0–7.5)	22	4	13	29 = Yes; 10 = No
Ex vivo	M = 1; F = 3	61.0 ± 4.8	21.8 ± 5.9	N/A	0	4	0	4 = Yes

Supplementary Table 3. Demographics of multiple sclerosis patients involved in the study. Mean and standard deviation for age and disease duration, and median and range for EDSS reported. EDSS = expanded disability status scale; MS = multiple sclerosis; RRMS = relapse remitting MS; PPMS = primary progressive MS; SPMS = secondary progressive MS.

	Company	Host / Clonality	Antigen Retrieval Method	Protein Blocking Reagent	Primary Antibody Concentration	Primary Antibody Inoculation	Secondary Antibody
Iba1	Wako	Rb, P	HIER with Citrate Buffer, 20"	Protein Block (Dako), 20" for HRP; 2.5% Horse Serum (Vector) for AP	1:400	1 hour, RT	Powervision Poly-HRP or ImmPRESS AP
MRP14	Dako	Ms, M	Proteinase K, 5"	Protein Block (Dako), 20" for HRP; 2.5% Horse Serum (Vector) for AP	1:400	1 hour, RT	Powervision Poly-HRP or ImmPRESS AP
CD3	Dako	Rb, P	HIER with Tris-EDTA Buffer, 45"	Protein Block (Dako), 20"	1:100	Overnight, 4ºC	Powervision Poly-HRP
PLP	BioRad	Ms, M	HIER with Citrate Buffer, 20"	Protein Block (Dako), 20"	1:200	1 hour, RT	Powervision Poly-HRP
GFAP	Dako	Rb, P	Proteinase K, 5"	Protein Block (Dako), 20"	1:400	1 hour, RT	Powervision Poly-HRP
ASPA	GeneTex	Rb, P	HIER with Citrate Buffer, 45"	Protein Block (Dako), 20"	1:1500	1 hour, RT	Powervision Poly-HRP
Olig2	EMD Millipore	Rb, P	None when double-staining	2.5% Horse Serum (Vector), 20"	1:200	1 hour, RT	ImmPRESS AP
TfR	ThermoFisher Scientific	Ms, M	HIER with Citrate Buffer, 45"	Background Buster (BioRad), 10"; Protein Block (Dako), 20"	1:100	Overnight, 4ºC	Powervision Poly-HRP
FpN	Abcam	Rb, P	HIER with Citrate Buffer, 45"	Background Buster (BioRad), 10"; Protein Block (Dako), 20"	1:100	Overnight, 4ºC	Powervision Poly-HRP
HpC	Abcam	Rb, P	HIER with Citrate Buffer, 45"	Background Buster (BioRad), 10"; Protein Block (Dako), 20"	1:100	Overnight, 4ºC	Powervision Poly-HRP
DMT1	Abcam	Rb, P	HIER with Citrate Buffer, 45"	Background Buster (BioRad), 10"; Protein Block (Dako), 20"	1:100	Overnight, 4ºC	Powervision Poly-HRP
Ferritin	Abcam	Rb, P	Proteinase K, 20"	Protein Block (Dako), 20"	1:100	1 hour, RT	Powervision Poly-HRP
SOD	Enzo	Rb, P	HIER with Citrate Buffer, 20"	Background Buster (BioRad), 10"; Protein Block (Dako), 20"	1:200	Overnight, 4ºC	Powervision Poly-HRP
DMT1	Abcam	Rb, P	HIER with Citrate Buffer, 45"	Background Buster (BioRad), 10"; Protein Block (Dako), 20"	1:100	Overnight, 4ºC	Powervision Poly-HRP
HIF-2a	GeneTex	Ms, M	HIER with Citrate Buffer, 20"	Background Buster (BioRad), 10"; Protein Block (Dako), 20"	1:200	Overnight, 4ºC	Powervision Poly-HRP

Supplementary Table 4. Immunohistochemistry methodology. For each of the immunohistochemical targets, respective companies, clonalities and hosts, and methods for antigen retrieval, blocking, and primary and secondary antibody inoculation are listed. HIER = heat-induced epitope retrieval; RT = room temperature; P = polyclonal antibody; M = monoclonal antibody; Rb = rabbit; Ms = mouse.