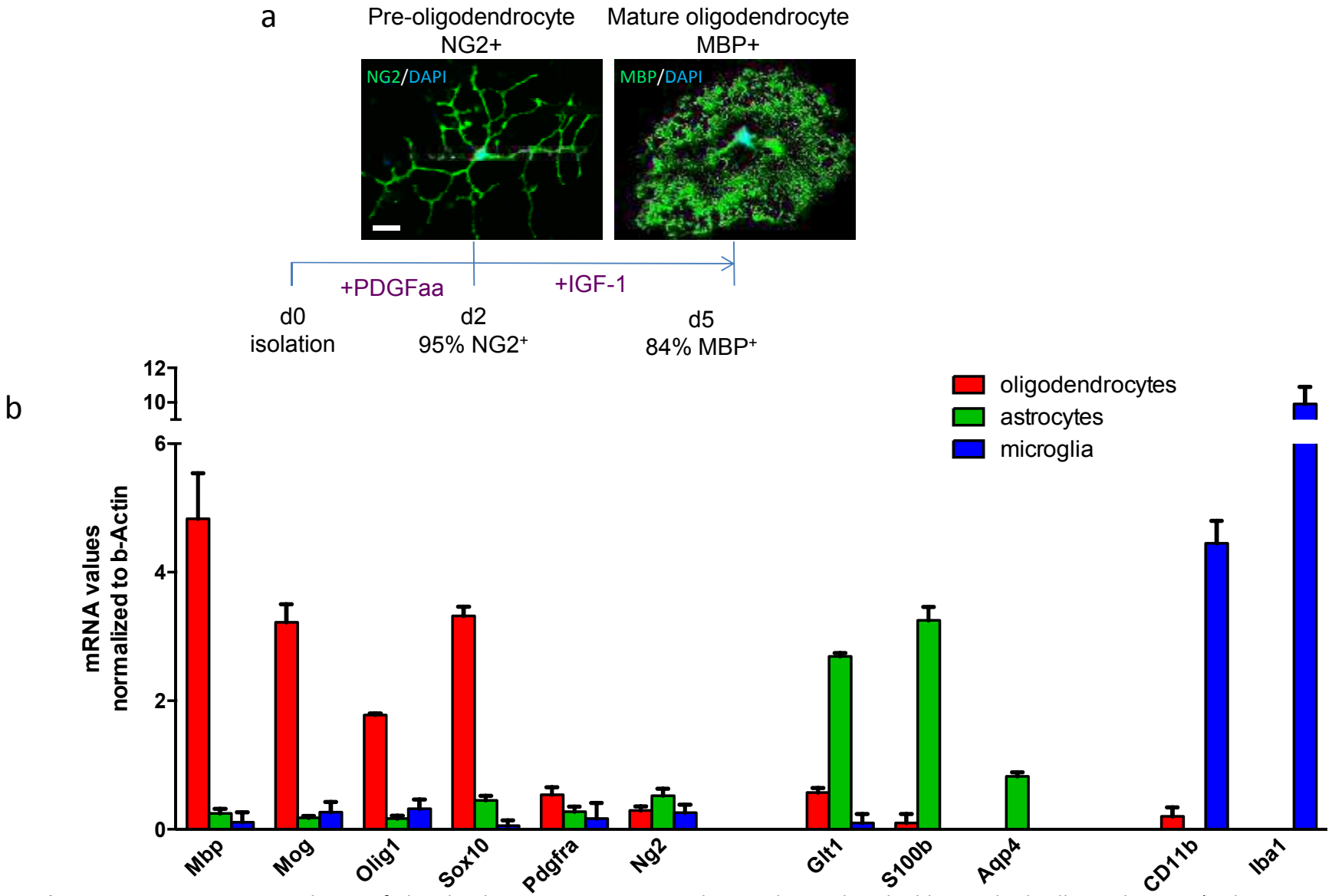
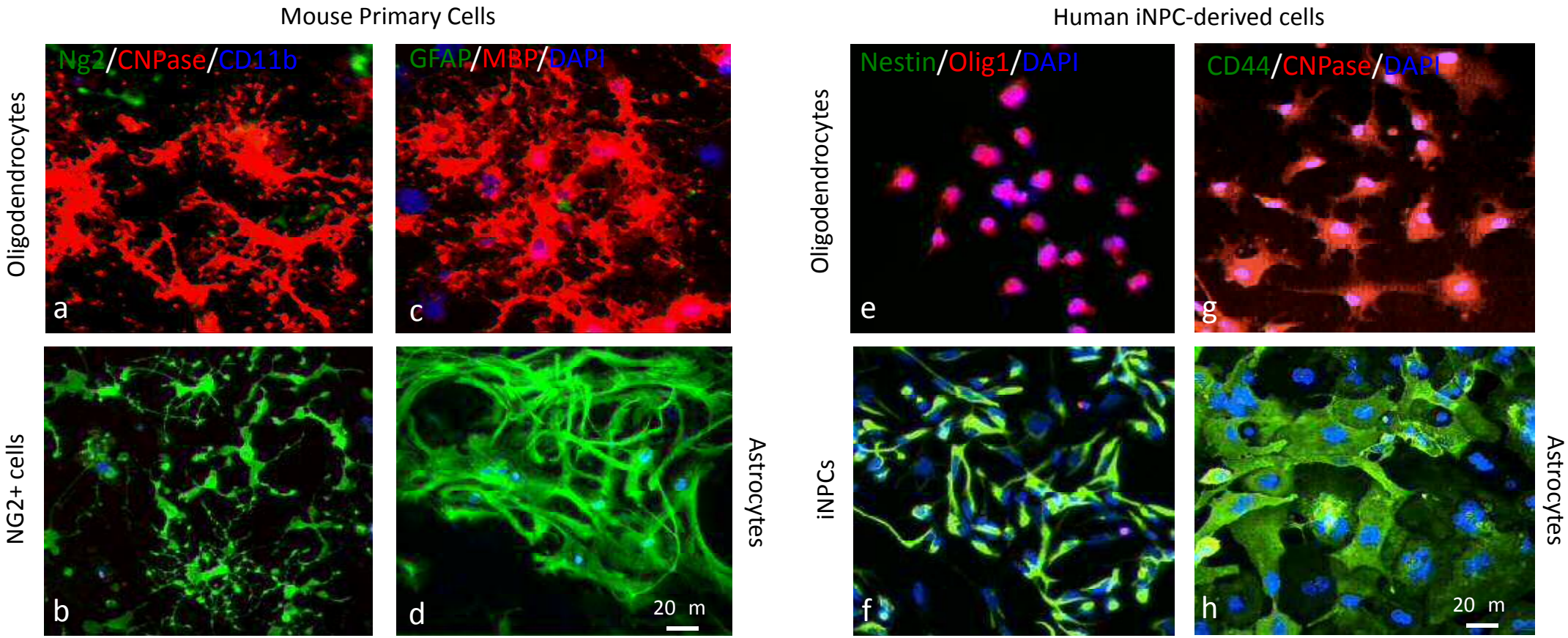


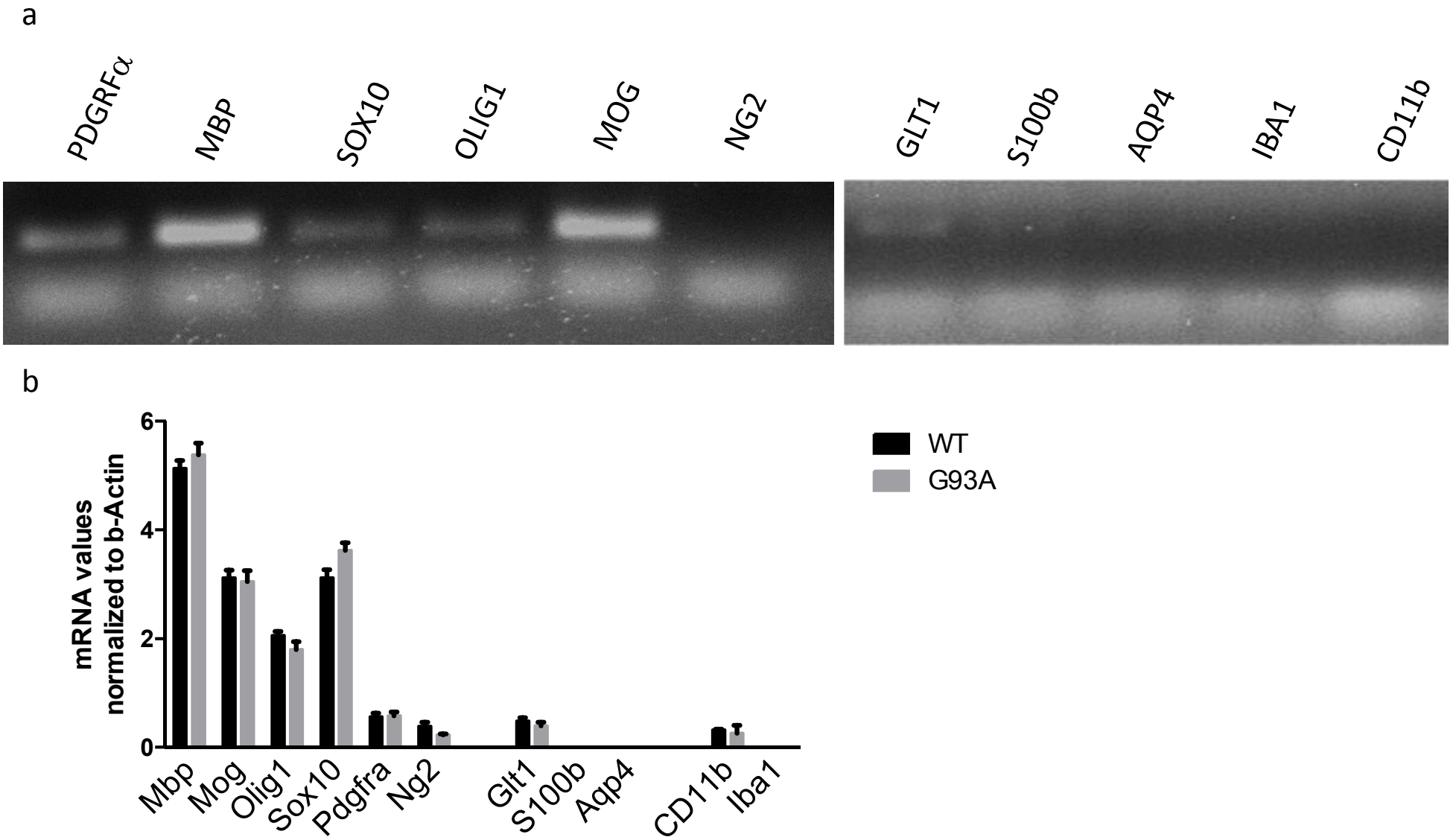
Supplementary Fig. 1 Primary cultures of oligodendrocytes, astrocytes and microglia produce highly enriched cell populations a) schematic representation of isolation of primary oligodendrocyte progenitors and subsequent differentiation. Bar=15 m b) quantification of each marker relative to b-Actin showing the expression levels of various oligodendrocyte, astrocyte and microglia markers normalised to cDNA from whole spinal cord homogenate. N=3, error bars=SD

	total cells	MBP+	Olig1+	Nestin+	NG2+	Iba1+	Glt1+	CD44	negative for all markers
mouse oligodendrocytes	400	336	310	0	64	0	0	0	0
human oligodndrocytes	400	384	346	0	0	0	0	0	16

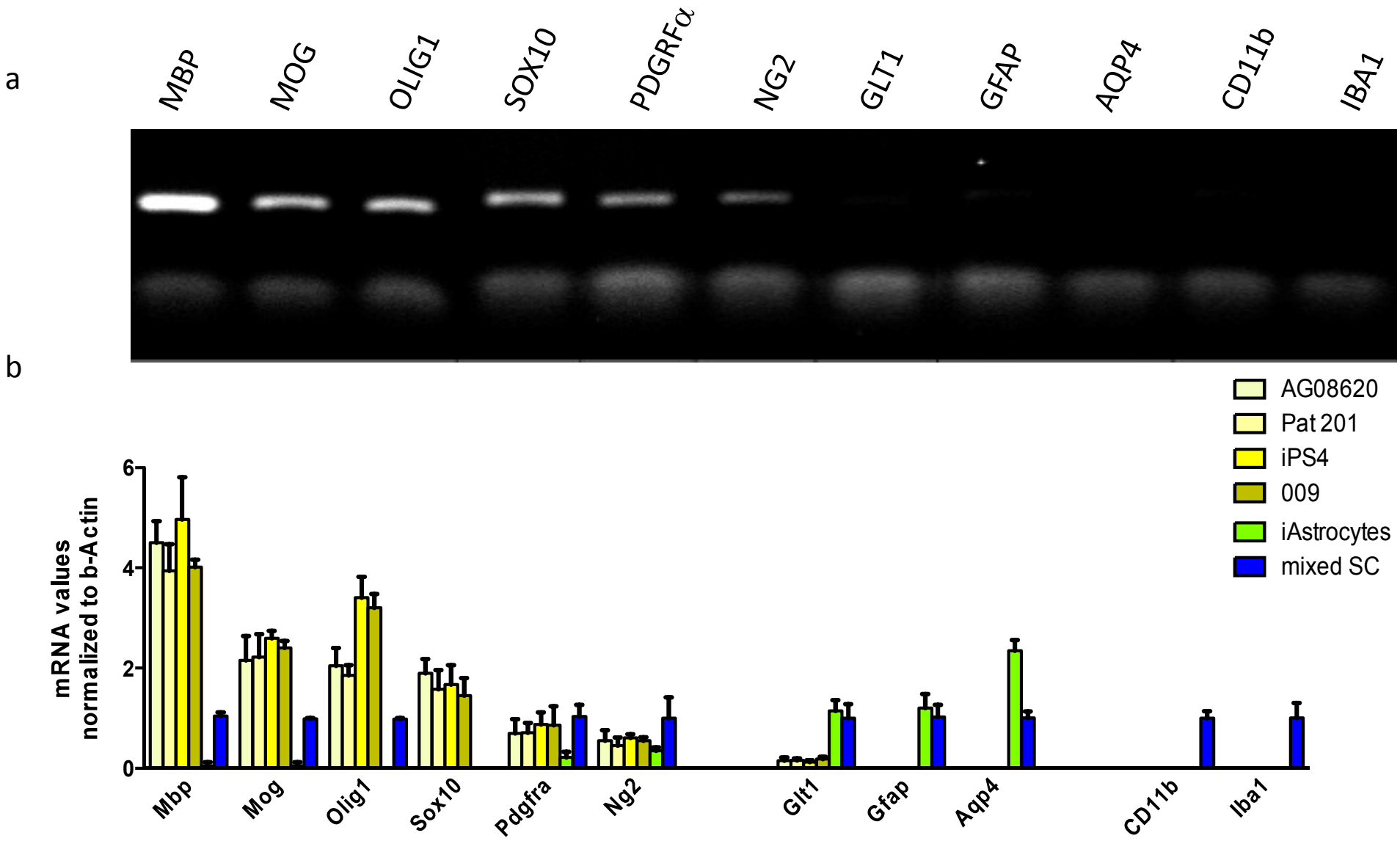
Supplementary Table 1. Number of mouse and human cells stained with different progenitor and glial markers and counted to assess culture purity at the end of the differentiation protocol.



Supplementary Fig 2. Mouse (a-d) and human oligodendrocytes (e-h) express prototypic cellular markers. Immunofluorescence shows high expression of oligodendrocytic markers like CNPase (a) and MBP (c) in mouse primary cell and minimal presence of early markers such as NG2 and absence of microglia (a,b) and astrocyte (c) contamination. Human oligodendrocytes express Olig1 and CNPase markers (e, g) and are negative for progenitor or astrocyte markers (f, h)



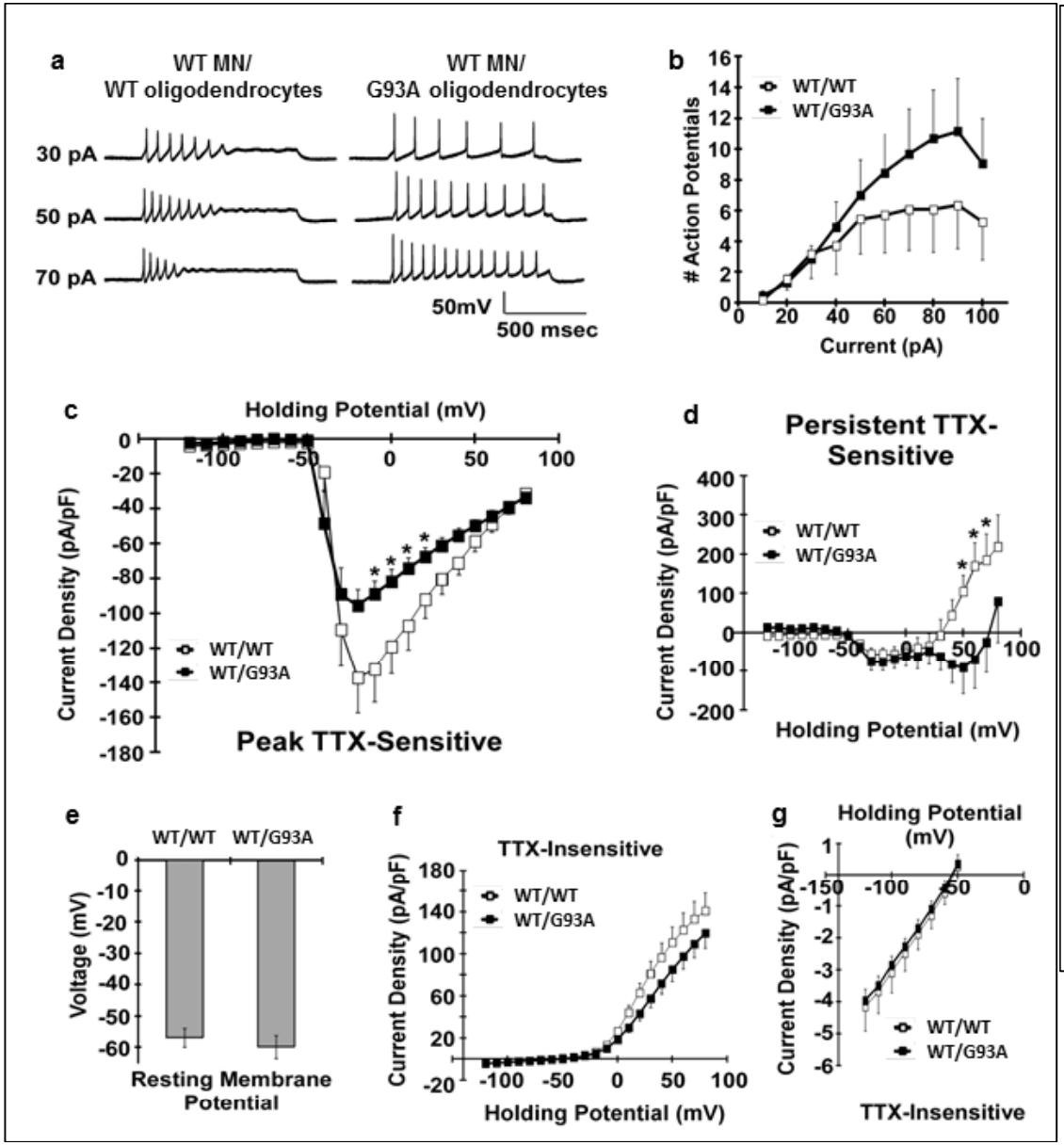
Supplementary Fig. 3 mSOD1G93A and WT oligodendrocytes express the same levels of cell-specific markers. a) PCR products from Q-PCR and b) quantification relative to b-Actin showing the expression levels of various oligodendrocyte, astrocyte and microglia markers normalized to whole spinal cord homogenates.



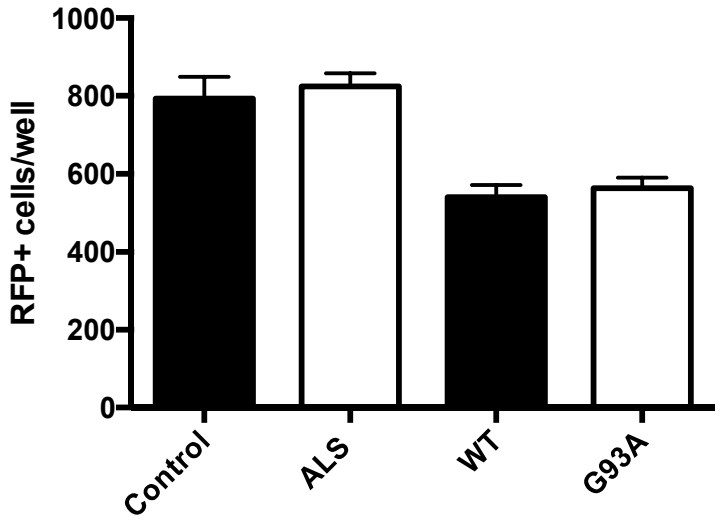
Supplementary Fig. 4 Human oligodendrocytes obtained from iNPCs or iPSCs express the same levels of cell-specific markers. a) PCR products from Q-PCR of the panel of markers tested iOligodencrocytes and b) quantification relative to b-Actin showing the expression levels of various oligodendrocyte, astrocyte and microglia markers in 4 different human Oligodendrocytes samples (in yellow), iAstrocytes derived from iNPCs and cDNA from whole spinal homogenate. Values are normalized to spinal cord homogenate values. N=3, error bar=SD

Annotation Cluster 1	Enrichment Score: 10.59			Count	P_Value	Benjamini
GOTERM_CC_FAT	organelle lumen	RT		369	7.5E-16	5.3E-13
GOTERM_CC_FAT	membrane-enclosed lumen	RT		374	1.1E-15	3.8E-13
GOTERM_CC_FAT	intracellular organelle lumen	RT		361	1.4E-15	3.3E-13
GOTERM_CC_FAT	nuclear lumen	RT		275	1.4E-8	1.2E-6
GOTERM_CC_FAT	nucleolus	RT		148	7.5E-8	5.1E-6
GOTERM_CC_FAT	nucleoplasm	RT		160	2.4E-4	5.3E-3
Annotation Cluster 2	**Enrichment Score: 8.35**			**Count**	**P_Value**	**Benjamini**
SP_PIR_KEYWORDS	mitochondrion	RT		188	2.2E-13	3.1E-11
GOTERM_CC_FAT	mitochondrial part	RT		142	3.9E-11	5.3E-9
GOTERM_CC_FAT	mitochondrion	RT		223	4.7E-10	5.3E-8
GOTERM_CC_FAT	mitochondrial matrix	RT		62	1.7E-7	1.0E-5
GOTERM_CC_FAT	mitochondrial lumen	RT		62	1.7E-7	1.0E-5
UP_SEQ_FEATURE	transit peptide:Mitochondrion	RT		103	4.0E-7	7.6E-4
SP_PIR_KEYWORDS	transit peptide	RT		103	7.9E-7	8.0E-5
Annotation Cluster 3	**Enrichment Score: 8.31**			**Count**	**P_Value**	**Benjamini**
GOTERM_CC_FAT	non-membrane-bounded organelle	RT		470	1.9E-11	3.2E-9
GOTERM_CC_FAT	intracellular non-membrane-bounded organelle	RT		470	1.9E-11	3.2E-9
GOTERM_CC_FAT	cytoskeleton	RT		236	3.4E-4	6.4E-3
Annotation Cluster 4	**Enrichment Score: 4.81**			**Count**	**P_Value**	**Benjamini**
GOTERM_BP_FAT	protein complex biogenesis	RT		111	1.6E-6	1.7E-3
GOTERM_BP_FAT	protein complex assembly	RT		111	1.6E-6	1.7E-3

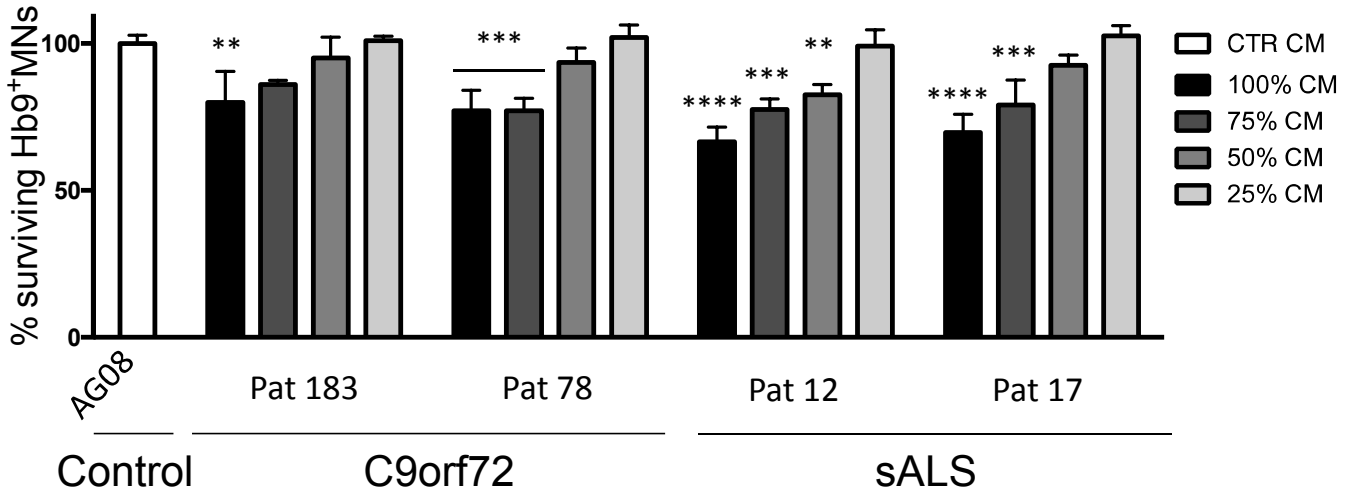
Supplementary Fig. 5 Gene enrichment analysis performed on 3361 transcripts differentially expressed ($p<0.001$) between iOligodendrocytes, iAstrocytes and fibroblasts. The analysis shows that the most enriched categories are involved in membrane and lumen maintenance and mitochondrial maintenance and function.



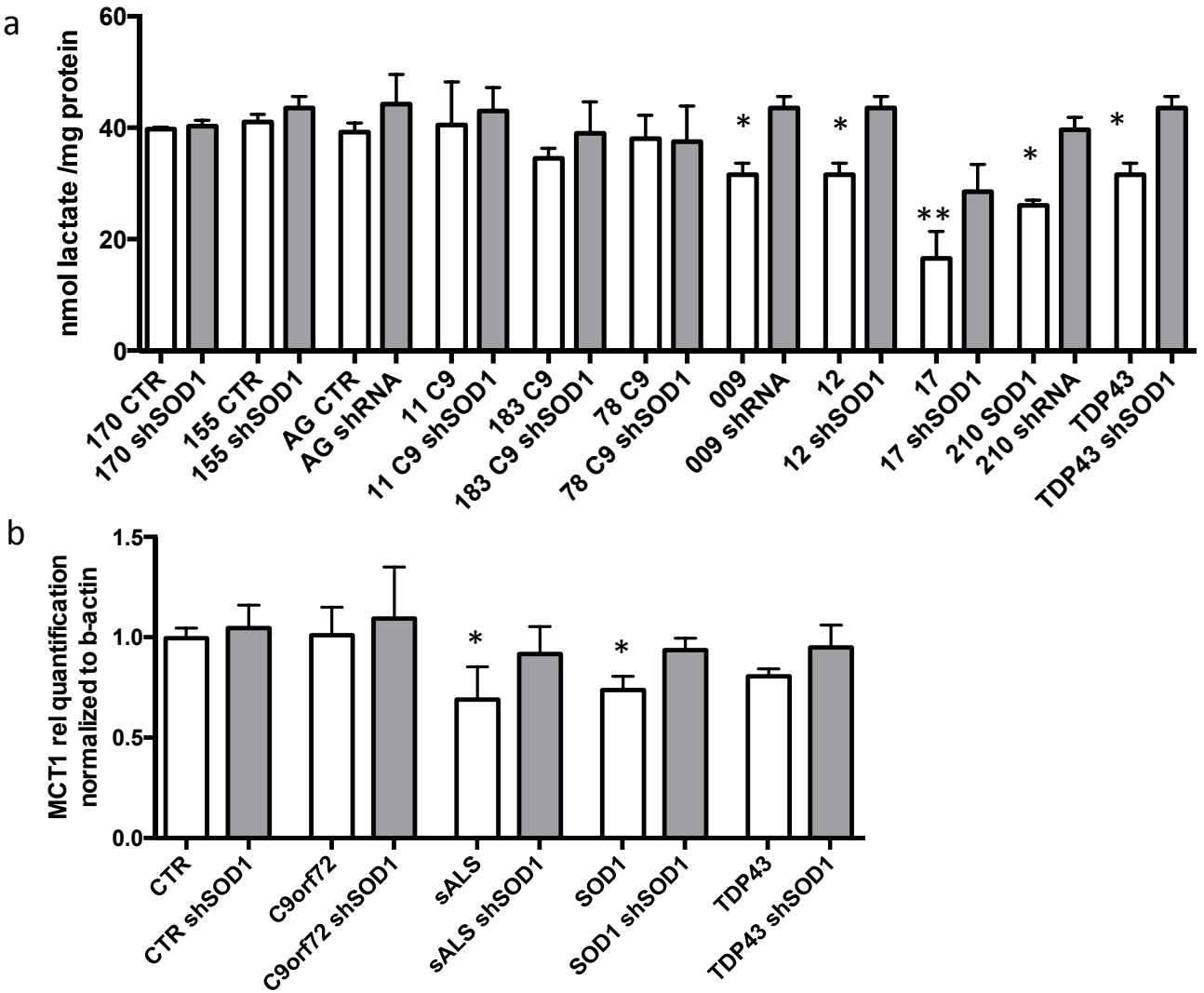
Supplementary Figure 6.Motor neurons co-cultured with ALS oligodendrocytes are hyperexcitable. Representative recordings of motor neurons co-cultured with either wild type oligodendrocytes (left) or mSOD1G93Aoligodendrocytes (right). Trains of action potentials were recorded in response to a 30pA, 50pA, and 70pA current injection as indicated (a). Mutant SOD1G93Aoligendrondrocytes affect motor neuron action potentials in response to current injection. Graph indicates the average number of action potentials evoked from 10-100pA current injection. n = 11-13, P<0.0001; Two Way ANOVA (b). Tetrodotoxin (TTX)-sensitive voltage-gated currents are different in motor neurons exposed to mSOD1G93A or wild type oligodendrocytes. Average of the peak TTX-sensitive current (which will include voltage-gated sodium currents) evoked with the indicated voltage step (n = 14) (c). TTX-sensitive persistent currents are different in motor neurons exposed to mSOD1G93A or wild type oligodendrocytes. Average of the sustained tetrodotoxin-sensitive current (which will include persistent voltage-gated sodium currents) evoked with the indicated voltage step and measured during the last 50ms of the voltage step (n = 13). By convention, inward currents are shown as negative values and outward currents are positive values. (d). Average resting membrane potential of wild type motor neurons co-cultured with either wild type or mSOD1G93A oligodendrocytes (n = 11-13, n.s.) (e). TTX-insensitive voltage-dependent currents are not different between motor neurons exposed to wild type or mSOD1G93A oligodendrocytes. Graphs represent the average current density of TTX-insensitive currents (f) and of leak currents (g) (n = 14). Recording for all the parameters have been collected from 3 independent co-cultures. Error bars represent the SEM.



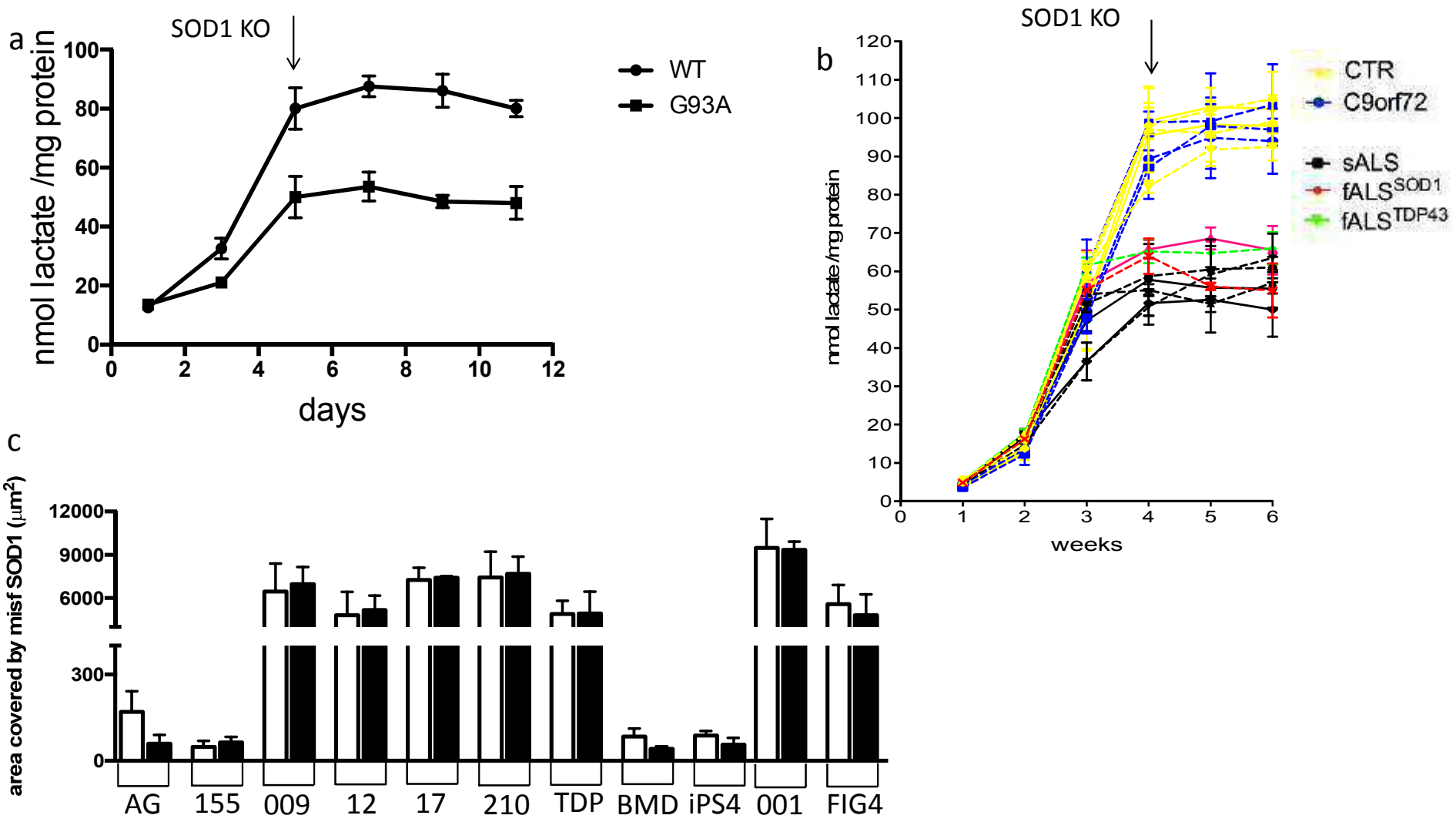
Supplementary Fig. 7 ALS Human and mouse oligodendrocytes do not degenerate during differentiation and co-culture. MBR-RFP+ oligodendrocyte counts from human control and patients and wild type (WT) and mutant $SOD1^{G93A}$ (G93A) mice at the end of co-culture. Each sample was analyzed in triplicate and data pooled in a single graph bar. N=15-35 for the human samples, N= 9 for muse samples. Error bar=SD



Supplementary Fig.8 Effect of human iOligodendrocyte conditioned medium (CM) on Hb9GFP^{+} MNs monocultures. Complete replacement of MN medium with oligodendrocyte conditioned medium from all cells derived from ALS patients results in a significant decrease in MN survival (black bars). This negative effect decreases as the % of CM added to the MN culture medium is reduced from 100% to 75% and 50%. Supplementation of MN culture medium with 25% iOligodendrocyte CM has no effect on MN survival.



Supplementary Fig. 9 Lactate release impairment is related to a decrease in lactate production (a) accompanied by decreased expression of the MCT1 lactate transporter (b). A) intracellular oligodendrocyte lactate levels measured using a colorimetric lactate assay (Abnova); n=3, error bar=SD. B) MCT1 expression levels relative to b-Actin measured via Q-PCR. Each sample was repeated in duplicate. N= 1- 3 depending on the genotype. Error bar=SD



Supplementary Fig. 10 SOD1 knockdown at the end of oligodendrocyte differentiation does not rescue impairments in lactate secretion and SOd1 aggregates. a) Lactate levels in WT and SOD1G93A oligodendrocyte conditioned medium do not vary after SOD1 knockdown at day 5. b) SOD1 knockdown in MBP+ oligodendrocytes does not result in lactate secretion increase for up to two weeks after treatment. c) SOD1 knockdown in MBP+ oligodendrocytes does not lead to a decrease in SOD1 misfolding.

Cell line	Diagnosis	Mutation	Age at diagnosis (y)	Gender	cell type received in lab	Source	Conversion method
AG08620	Non-ALS	—	64	Female	Fibroblasts	Coriell Institute	iNPC
155	Non-ALS	—	42	Male	Fibroblasts	P.J.S.	iNPC
170	Non-ALS	—	65	Male	Fibroblasts	P.J.S.	iNPC
iPS4	Non-ALS	—	na	na	iPS	George Daley-HSCI	iPS
GM23262	BMD	DMD	6	Male	iPS	Coriell Institute	iPS
ND29505	fALS	SOD1D90A	56	Male	Fibroblasts	Coriell Institute	iNPC
ND32947	fALS	TDP43G298S	63	Male	Fibroblasts	Coriell Institute	iNPC
ALS 78	fALS	C9ORF72	68	Male	Fibroblasts	P.J.S.	iNPC
ALS 183	fALS	C9ORF72	51	Male	Fibroblasts	P.J.S.	iNPC
ALS 11	sALS	C9ORF72	52	Male	Fibroblasts	S.J.K.	iNPC
ALS 12	sALS	na	29	Male	Fibroblasts	S.J.K.	iNPC
ALS 17	sALS	na	47	Male	Fibroblasts	S.J.K.	iNPC
ALS 002	sALS	na	60	Male	Fibroblasts	S.J.K.	iPS, iNPC
ALS 009	sALS	na	61	Female	Fibroblasts	S.J.K.	iPS, iNPC
ALS001	sALS	na	68	Female	Fibroblasts	S.J.K.	iPS
ND35669	fALS	FIG4C27T	66	Female	iPS	Coriell Institute	iPS

Supplementary Table 2. Specifications of the cell lines used in this study, including mutations and protocol used for conversion from fibroblasts. PJS = Pamela J. Shaw; S.J.K = Stephen J. Kolb.

Supplementary Table 3. Genes involved in membrane maintenance and myelin production with increased expression in iOligodendrocytes over iAstrocytes and fibroblasts

ID	Gene Title	Gene Symbol	p-value
204205_at	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	APOBEC3G	4.78E-05
203381_s_at	apolipoprotein E	APOE	3.35E-05
203382_s_at	apolipoprotein E	APOE	0.000673
209546_s_at	apolipoprotein L, 1	APOL1	0.00326
221653_x_at	apolipoprotein L, 2	APOL2	0.000529
221087_s_at	apolipoprotein L, 3	APOL3	0.000185
200602_at	amyloid beta (A4) precursor protein	APP	0.000115
214953_s_at	amyloid beta (A4) precursor protein	APP	0.00119
213702_x_at	N-acylsphingosine amidohydrolase (acid ceramidase) 1	ASAH1	0.00242
229958_at	ceroid-lipofuscinosis, neuronal 8 (epilepsy, progressive with mental retardation)	CLN8	0.006861
202419_at	3-ketodihydrosphingosine reductase	KDSR	0.000501
234985_at	low density lipoprotein receptor class A domain containing 3	LDLRAD3	0.002348
214045_at	lipoic acid synthetase	LIAS	0.000421
205571_at	lipoyltransferase 1	LIPT1	0.00066
203548_s_at	lipoprotein lipase	LPL	0.00032
203549_s_at	lipoprotein lipase	LPL	0.001893
1554544_a_at	myelin basic protein	MBP	0.006448
210136_at	myelin basic protein	MBP	9.62E-05
225407_at	myelin basic protein	MBP	0.005022
232148_at	neutral sphingomyelinase (N-SMase) activation associated factor	NSMAF	0.004366
202075_s_at	phospholipid transfer protein	PLTP	0.001798
212321_at	sphingosine-1-phosphate lyase 1	SGPL1	0.000865
212322_at	sphingosine-1-phosphate lyase 1	SGPL1	1.09E-05

Antibody	Provider	cat #	Dilution
NG2	Millipore	AB5320	1:400
MBP	Abcam	AB106583	1:300
IBA1	Fisher	NC9288364	1:400
GalC	Millipore	AB142	1:300
Pax6	Abcam	AB5790	1:200
Nestin	Millipore	AB5922	1:500

Supplementary Table 4. Antibodies used for cell characterization

Supplementary Materials and Methods

Mouse cultures

Primary cultures of cerebral cortical oligodendrocytes were prepared from c57/bl6 SOD1^{G93A} mice and littermate newborn mice (1-3 days old). Pups were screened for human SOD1 transgene at P1 and 3 brains from mSOD1 or control mice were pooled together.

Mixed cortical cultures were grown to confluence in DMEM containing 10% fetal bovine serum in T75 flasks and oligodendrocyte progenitors and microglia were separated from the astrocyte monolayer through shaking (250 rpm, 37C O/N). The following morning the supernatant was collected and plated in an untreated Petri dish for 40 minutes to allow microglia to attach. Oligodendrocyte progenitor cells (OPCs) were collected in the supernatant, spun at 200g for 4 min, counted and plated in 96well plates for co-culture (30,000 cells/well) or on 1cm^2 coverslips for staining and electrophysiology recordings (150,000 cells/well).

OPCs were cultured in DMEM with 10% serum for 4h. Subsequently, the cells were washed twice with PBS to remove traces of serum and the medium was switched to DMEM/F12 supplemented with 2% B27, 20 ng/mL PDGFaa for 48h. The cells were then cultured without PDGFaa and with IGF-1 (20ng/ml) for 72h.

For SOD1 knock down experiments, an adenovirus containing a SOD1 shRNA sequence was used, for control an adenovirus containing the RFP sequence was used. Cells were infected either at day of plating O/N or on day 4 of differentiation (48h before plating MN).

Human cell culture and differentiation Human skin fibroblast samples were obtained from The Ohio State University ALS/MND Clinic, as well as Prof. Pamela Shaw (University of Sheffield, Sheffield, United Kingdom) and from established tissue banks as shown in See SI Appendix Table S2 (Coriell Institute). Informed consent was obtained from all subjects before sample collection. Induced pluripotent stem cells (iPSC) and induced neural progenitors (iNPC) were obtained as described in Hester et al(1) and Meyer et al(2).

NPCs and iNPCs were plated in NPC medium supplemented with FGF2 and differentiation to oligodendrocytes was started when cells were about 80% confluent. On day 0 of differentiation, NPC medium was switched to differentiation medium (Neurobasal supplemented with 2% B27, 10mg/ml FGF2 and 15 ng/mL PDGFaa) for 1 week. After 1 week, the cells were cultured with decreased amounts of PDGFaa (10ng/ml) and IGF-1 (20ng/ml) for 2 weeks. In the last 10 days IGF-1 concentration was increased to 50 ng/mL and PDGFaa was depleted from the medium.

Several different protocols have been published for oligodendrocyte differentiation from human iPS cells. They all vary in length, from 47 days to differentiate iPSCs into O4+ cells(3), 95 days from iPSCs to MBP+ cells(4) to 180 days from iPSCs to O4+/MBP+ cells ENREF 40(5). Although it is difficult to compare protocols starting from different cells types, i.e. iPSCs vs NPCs/iNPCs, our protocol is very similar in length and differentiation factors utilized, including PDGFaa and IGF-1, to the publication by Douvaras et al and Livesey et al. (4, 6). The authors, in fact, report a 30-40 day differentiation step from progenitors cells to oligodendrocytes. Comparing our protocol to others already published, one of the main differences is the concentration of IGF-1 used to induce the oligodendrocyte phenotype. We found, in fact, that in our model IGF-1 is essential for cell differentiation towards the oligodendrocyte fate, as described in Hsieh et al(7). We initially tested in parallel differentiation efficiency using different concentrations of IGF-1. We tested 3 conditions: no IGF-1, IGF-1 10ng/ml or IGF-1 20ng/ml during week 2 and 3. IGF-1 concentrations were respectively increased to 10ng/ml, 20ng/ml or 50ng/ml in the last 10 days. The protocol leading to the highest number of MBP+ cells and highest purity was the protocol with the highest concentrations of IGF-1. We, therefore, adopted that protocol for the whole study.

For SOD1 knock down experiments SOD1 was knocked down at the OPC stage (i.e., 7 days into the differentiation protocol) or at the final stage of differentiation (i.e. 30 days post NPC plating) 48h before plating MN.

ES Motor Neuron Differentiation. Mouse embryonic stem cells expressing GFP under the MN-specific promoter HB9 (HBG3 cells; kind gift from Tom Jessell) were cultured on primary mouse embryonic fibroblasts (Millipore). For

differentiation into MNs, cells were lifted with trypsin and resuspended in DFK10 culture medium consisting of knockout DMEM/F12, 10% knockout serum replacement, 1% N2, 0.5% L-glutamine, 0.5% glucose (30% in water), and 0.0016% 2-mercaptoethanol. The cells were plated on non-adherent Petri dishes to allow formation of embryoid bodies. After 1 d of recovery, 2 μM retinoic acid (Sigma) and 2 μM purmorphamine (Calbiochem) were added freshly every day with new medium. After 5 d of differentiation, the embryoid bodies were dissociated and sorted for GFP on a BD FACSVantage/DiVa sorter and collected in serum-free motor neuron medium.

Coculture of Motor Neurons and Oligodendrocytes. Mouse oligodendrocyte progenitors were plated in 96-well plates coated with poly-ornithin/laminin and differentiated in situ as described above. Human NPCs or iNPCs were plated on 1cm^2 coverslips coated with fibronectin (2.5 μg/mL; Millipore) at a density of 40,000 per well and differentiated for 30 days. Only coverslips with 60-65% confluent cells were used for co-culture. On day of co-culture FACS-sorted GFP-positive MNs were resuspended in MN medium without horse serum consisting of DMEM/F12, 2% N2, 2%B27 plus GDNF (Invitrogen; 10 ng/mL), BDNF (Invitrogen;10 ng/mL), CNTF (Invitrogen; 10 ng/mL) and IGF-1 (Invitrogen; 10 ng/mL) and added to the oligodendrocyte at a density of 10,000 per well in 96 well plates and 40,000 per well on 1cm^2 coverslips.

For lactate supplementation studies, 1mM or 2mM lactate was added to the co-cultures on the same day motor neurons were plated.

Each plate was scanned every day with the fully automated IN CELL 6000 confocal plate reader to capture GFP-positive cells. The INCELL Developer and Analyzer software were used to create whole-well pictures and count MNs. The operator analyzing the data was blinded for sample genotype and treatment.

Motor Neuron monocultures. Hb9GFP MNs were plated after sorting at a density of 10,000 MN/well in 96 well plates. MNs were plated in MN medium for 24h. After 24h, plates were scanned using the IN CELL 6000 plate reader to assess the number of cells before treatment. After scanning, medium was changed to 100%, 75%, 50% or 25% oligodendrocyte medium conditioned for 24h and supplemented with 2% horse serum. Medium was always collected

at the end of oligodendrocyte differentiation, day 6 through 11 for mouse cultures and week 5 to 6 for human cultures.
Medium was replaced with fresh conditioned medium every 48h.

Immunofluorescence. Cells were fixed with 4% paraformaldehyde for 15 min and washed 3× with Tris-buffered saline (TBS) before the blocking solution consisting of TBS with 10% donkey serum, 0.1% Triton X-100, and 0.1% Tween-20 was applied for 1 h. All primary antibodies were diluted in blocking solution and their dilution and provider are listed in See SI Appendix Table S4. Incubation of the primary antibody was performed overnight at 4 °C. The next day, cells were washed 3× in TBS before the secondary antibody and DAPI diluted in blocking solution was applied for 1.5 h at room temperature.

RNA Isolation and RT-PCR/Quantitative RT-PCR. RNA was harvested from cultured cells using the RNAeasy Mini kit (Qiagen), and total RNA was reverse-transcribed with RT2 First Strand Kit (SABiosciences) according to the manufacturer's instructions. PCR was performed with PCR master mix from Promega. Real-time quantitative PCR reactions were performed using RT2 Real-Time SYBR Green/Rox PCR Master Mix (SABiosciences), and PCR arrays were run on an ABI Prism 7000. Mouse and human primers were optimized using whole spinal cord extracts.

Electrophysiology. Recordings were performed on motor neurons in co-culture with mouse mSOD1 or WT oligodendrocytes 7 days post-plating. Neurons were continuously superfused with the extracellular solution containing 115 mM NaCl, 2 mM KCl, 1.5 mM MgCl2, 3 mM CaCl2, 10 mM HEPES, and 10 mM Glucose (pH 7.4). Glass electrodes (3-4 Mohms) were filled with the pipette solution containing 4 mM NaCl ,115 mM K-gluconate, 1.5 mM MgCl2, 10mM N-2-Hydroxyethylpiperazine-N'-2-Ethanesulfonic Acid (HEPES), and 0.5 mM ethylene glycol tetraacetic acid (EGTA), (pH 7.3). Data were collected using an Axopatch 200B amplifier, Digidata 1322A, and a Dell PC running Clampex 9 (Molecular Devices, Sunnyvale, CA). After whole-cell access was achieved, cells typically had a patch resistance >100 MOhm and series resistance was compensated by 40-50%. For analysis of voltage-gated currents, the cells were held at -70 mV and stepped in 10 mV increments from -120 mV to 80 mV for 400 ms. The voltage steps were performed in both the presence and absence of tetrodotoxin (TTX; 500nM).

TTX-sensitive currents were isolated by subtracting the currents recorded in the presence of TTX from those recorded in the absence of TTX. Transient TTX-sensitive current was quantified from the peak current amplitude and TTX-sensitive sustained current was quantified by averaging current during the final 50 ms of each voltage step. Leak currents were quantified in the presence of TTX in the range of -120 mV to -50 mV. Voltage-gated potassium currents were quantified in the presence of TTX by the current during the final 50 msof each voltage step. Membrane excitability was measured using current clamp. Cells received current injections in 10pA increments from 0 to 100 pA for either 300ms to 1 s to elicit action potentials. To account for differences in cell size, currents are reported as current densities (pA/pF).Data was analyzed using 2-way ANOVA with Bonferoni post hoc.

Quantification of SOD1 levels. To evaluate the levels of SOD1 knockdown in mouse and human oligodendrocytes, SOD1 isozyme was analyzed by ELISA (Abnova). Elisa was performed in 75 ng of cell lysate following manufacturer's recommendations.

Quantification of lactate levels. To evaluate the level of lactate in the oligodendrocyte growth medium, cells were differentiated for 5 days (mouse) or 30 days (human) as described in 96 or 24well plates. Mouse CM was collected for assay every 48h for a maximum of 11 days, while human CM was collected every week from NPC plating for a maximum of 6 weeks (4 weeks of differentiation + 2 weeks). On the day of the experiment, the culture medium was replaced with 500 µl of fresh medium. Oligodendrocytes were incubated for 24 h at 37°C in a water-saturated atmosphere containing 5% CO2/95% air. After 24 h, the supernatant was collected and centrifuged at 400g for 4 min at 4°C, filtered through a 0.2μm filter and stored on ice. The conditioned medium (50 µl) was used for measurement of lactate according to the manufacturers' instructions (Lactate Fluorimetric kit, Abnova KA0833). Lactate levels were normalized to cell protein.

ImageJ analysis. For each coverslip, images of 20 random fields were collected at 40x magnification. Pictures were acquired using the Openlab software (Improvision) and the fluorescence intensity per cell was analyzed

using the particle analysis function of ImageJ programme developed by Wayne Rasband (NIH, http://rsb.info.nih.gov/ij/).

Microarray analysis. RNA was isolated using Trizol from 4 oligodendrocyte lines differentiated for 4 weeks and kept in culture for one extra week post-differentiation in a 10cm Petri dish or 4 iAstrocytes lines differentiated for 1 week as previously described (2). RNA quantity and quality was assessed on the Nanodrop spectrophotometer and Agilent Bioanalyser, respectively, to ensure all samples were of comparable and sufficient quality to proceed (RIN<8). RNA was biotin-labelled, fragmented for 15 min and hybridized to the Human Genome U133 Plus 2.0 GeneChips, according to Affymetrix protocols. GeneChips were washed and stained in the Fluidics System 400 before being scanned in the GeneChip 3000 Scanner. Microarray chip quality control was performed using the Affymetrix Expression Console software and microarray data analysis was performed using Qlucore after normalization across all GeneChips using the RMA algorithm. Batch and disease effects were normalized using a general linear model embedded in the programme and ONE-way ANOVA with multiple group analysis correction was used to identify significantly differentially expressed transcripts. Qlucore was used also for Principal Component Analysis (PCA) and hierarchical clustering. The online Database for Annotation, Visualization and Integrated Discovery (DAVID) (Dennis *et al.*, 2003; Huang da *et al.*, 2009), Biocarta and Kegg were used to assign Gene Ontology terms, perform gene enrichment analysis and pathway analysis.

Statistical Analysis. Statistical analysis was performed by one-way ANOVA unpaired t test for mean differences between the average of all converted control lines versus each individual ALS line (GraphPad Prizm Software). All experiments were performed minimum in triplicate, quadruplicate, or more.

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