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Supplemental Information

LRRK2 Antisense Oligonucleotides Ameliorate α-Synuclein Inclusion Formation in a Parkinson's Disease Mouse Model

Hien Tran Zhao, Neena John, Vedad Delic, Karli Ikeda-Lee, Aneeza Kim, Andreas Weihofen, Eric E. Swayze, Holly B. Kordasiewicz, Andrew B. West, and Laura A. Volpicelli-Daley

Fig. S1

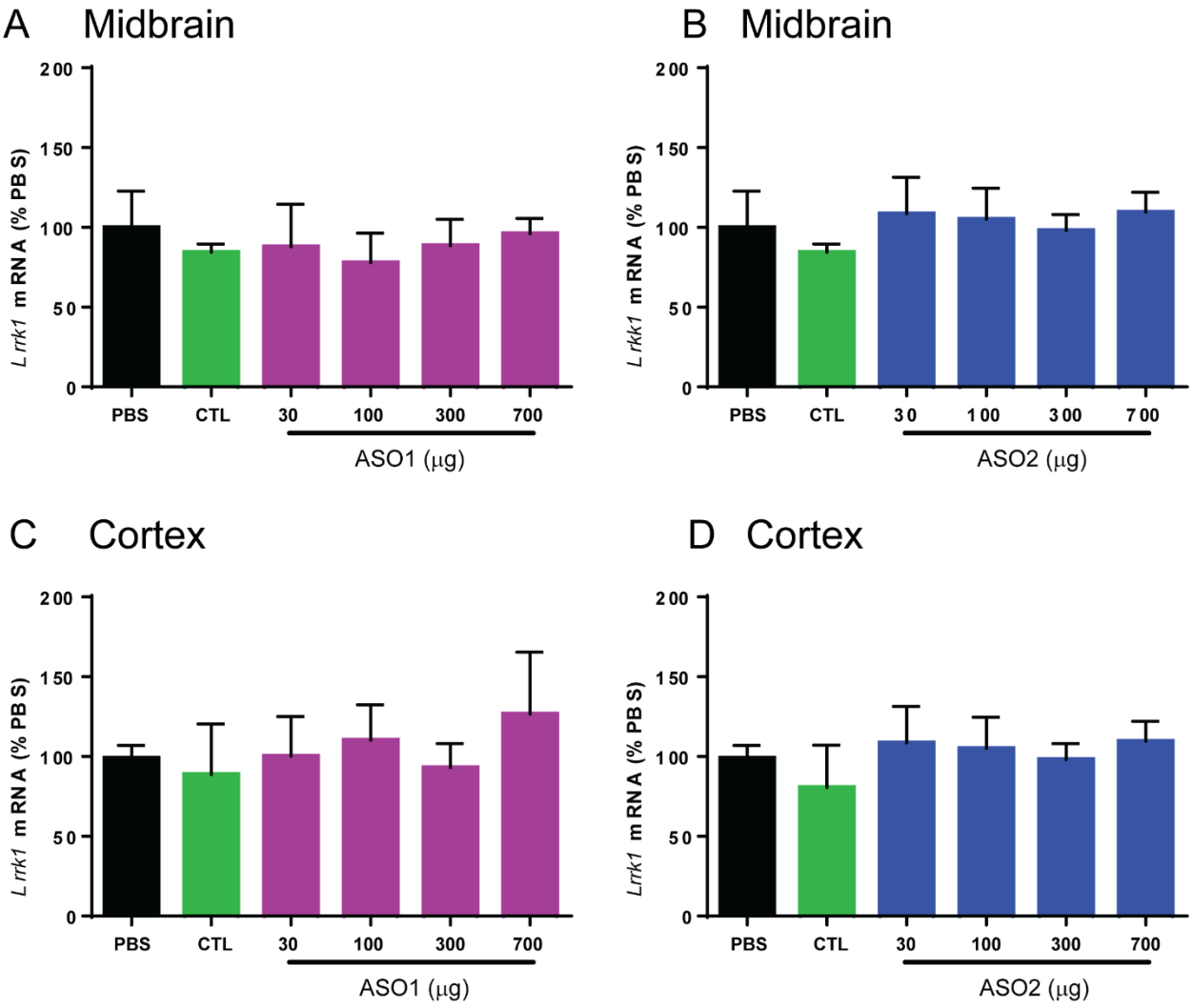

Fig. S1. No change in *Lrrk1* mRNA levels in the midbrain and cortex following LRRK2 ASO treatment. C57BL/6J mice received ICVB treatments with PBS (N=3), 700 µg CTRL (N=3), or LRRK2 ASO1 (N=3), or LRRK2 ASO2 (N=3) at 30, 100, 300 or 700 µg, respectively. Fourteen days later, brains were dissected and *Lrrk1* mRNA was quantified by RT-qPCR in the midbrain (**A,B**) and cortex (**C,D**) Data represents % PBS +/- SEM. LRRK2 ASO-treated groups were compared to PBS or CTL-treated groups using one-way ANOVA with Tukey's post-test.

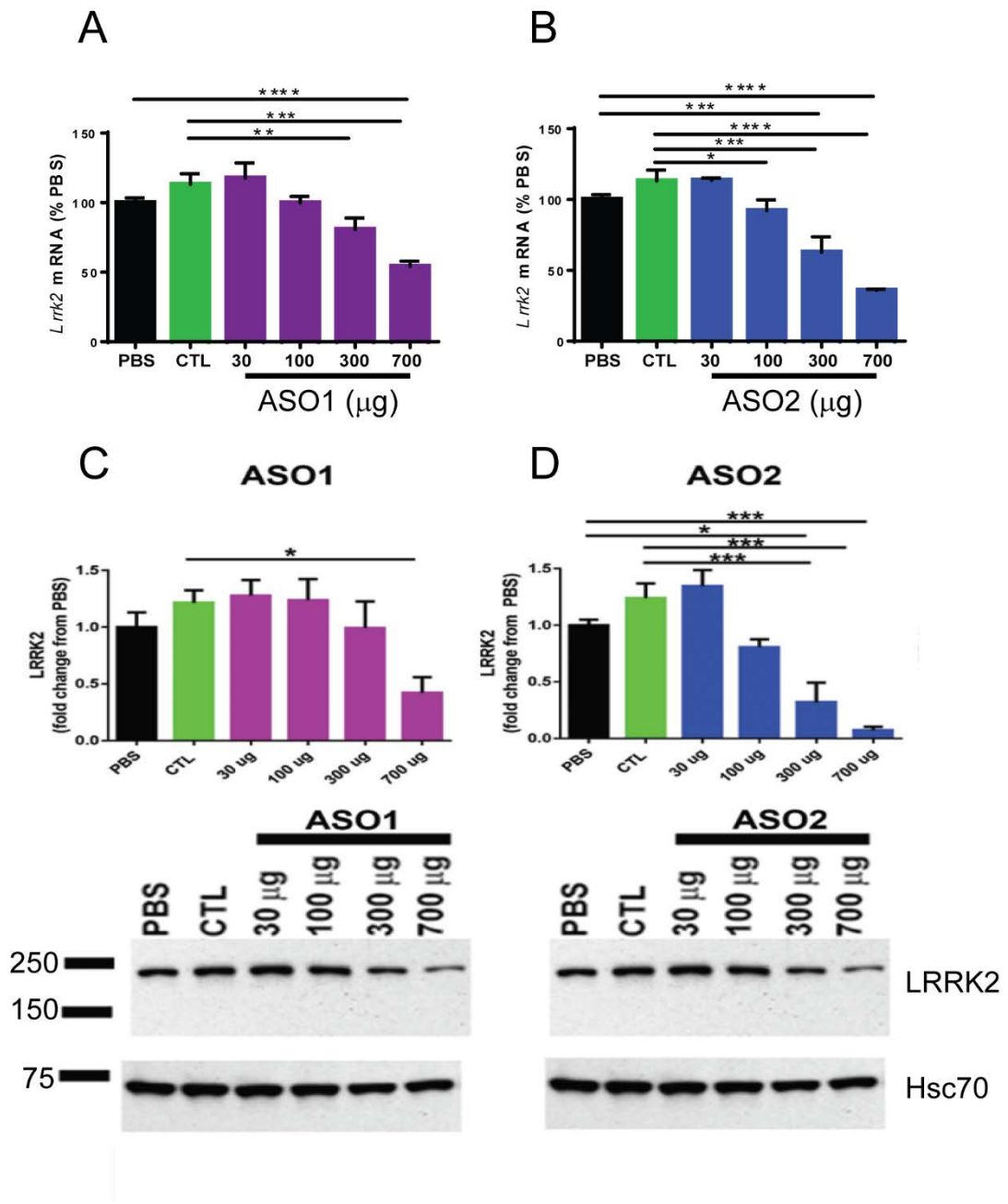

Fig. S2. Dose-dependent reduction of *Lrrk2* mRNA and LRRK2 protein in the cortex in LRRK2 ASO-treated mice. A,B. C57BL/6J mice received ICVB treatments with PBS (N=3), 700 µg CTRL (N=3), or LRRK2 ASO1 (N=3), or LRRK2 ASO2 (N=3) at 30, 100, 300 or 700 µg, respectively. Fourteen days later, brains were dissected. *Lrrk2* mRNA in the cortex was

quantified by RT-qPCR. **C,D.** Cortex homogenates from treated mice were immunoblotted for total LRRK2. HSC70 was used as a loading control. Bands from the LRRK2 immunoblots were quantified using ImageJ and normalized to HSC70. Data represents mean fold change relative PBS +/- SEM. LRRK2 ASO-treated groups were compared to PBS or CTL-ASO groups using one-way ANOVA with Tukey's post-test. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$.

Fig. S3

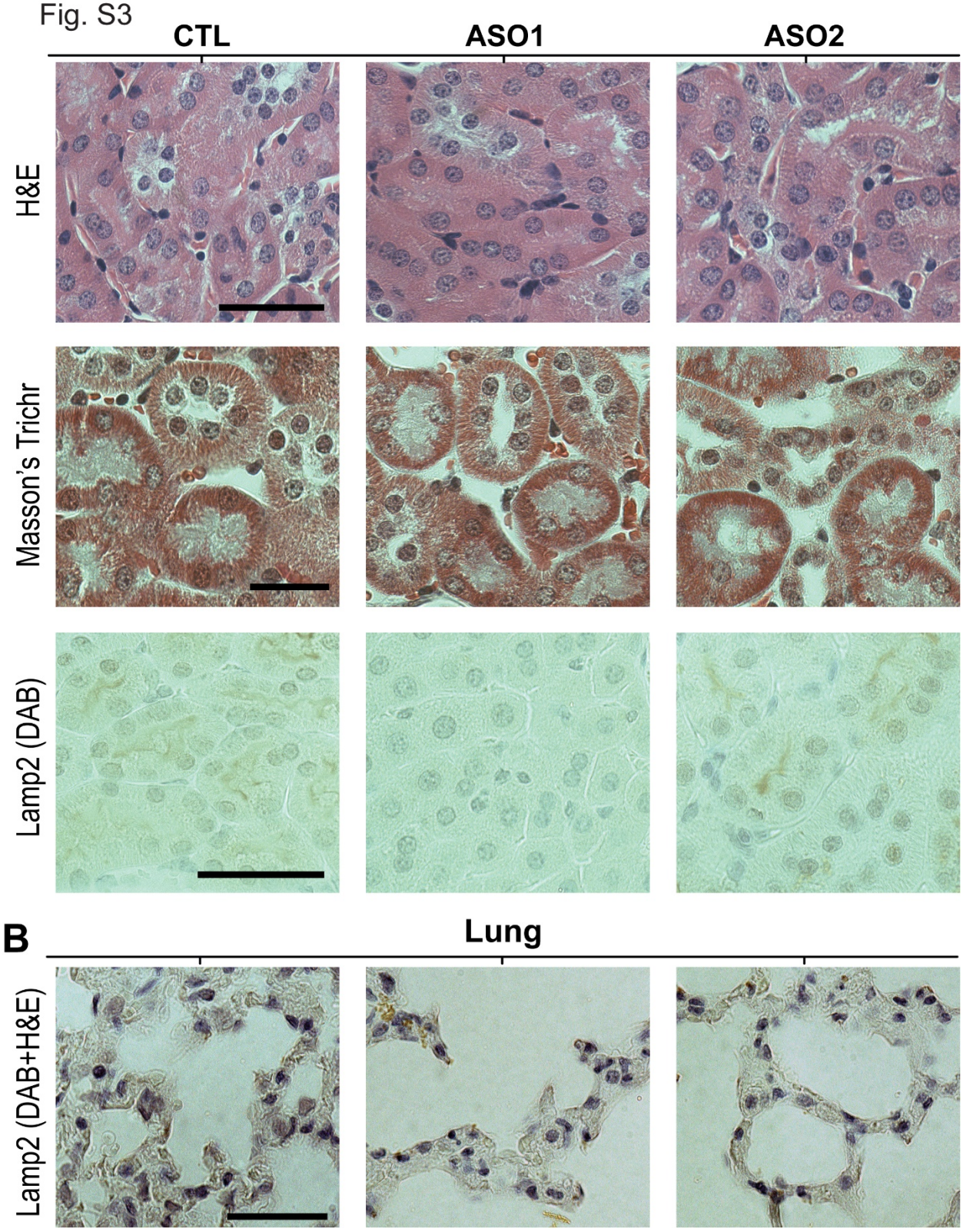

Figure S3. No histological change observed in kidney and lung following central administration of LRRK2-ASOs. **A.** To visualize the presence of vacuoles in proximal kidney epithelial cells, sections from kidney from ICVB treated mice receiving CTRL, LRRK2 ASO1 or LRRK2 ASO2 were stained using H&E, or **B.** Masson's Trichrome stain to visualize protein deposits. **C.** LAMP2 immunohistochemistry was also performed to visualize late endosomes/lysosomes in tubule cells. Sections shown are representative from dozens of sections cut through the kidney and lung from at least three animals from each group. Scale bars are 100 µm.

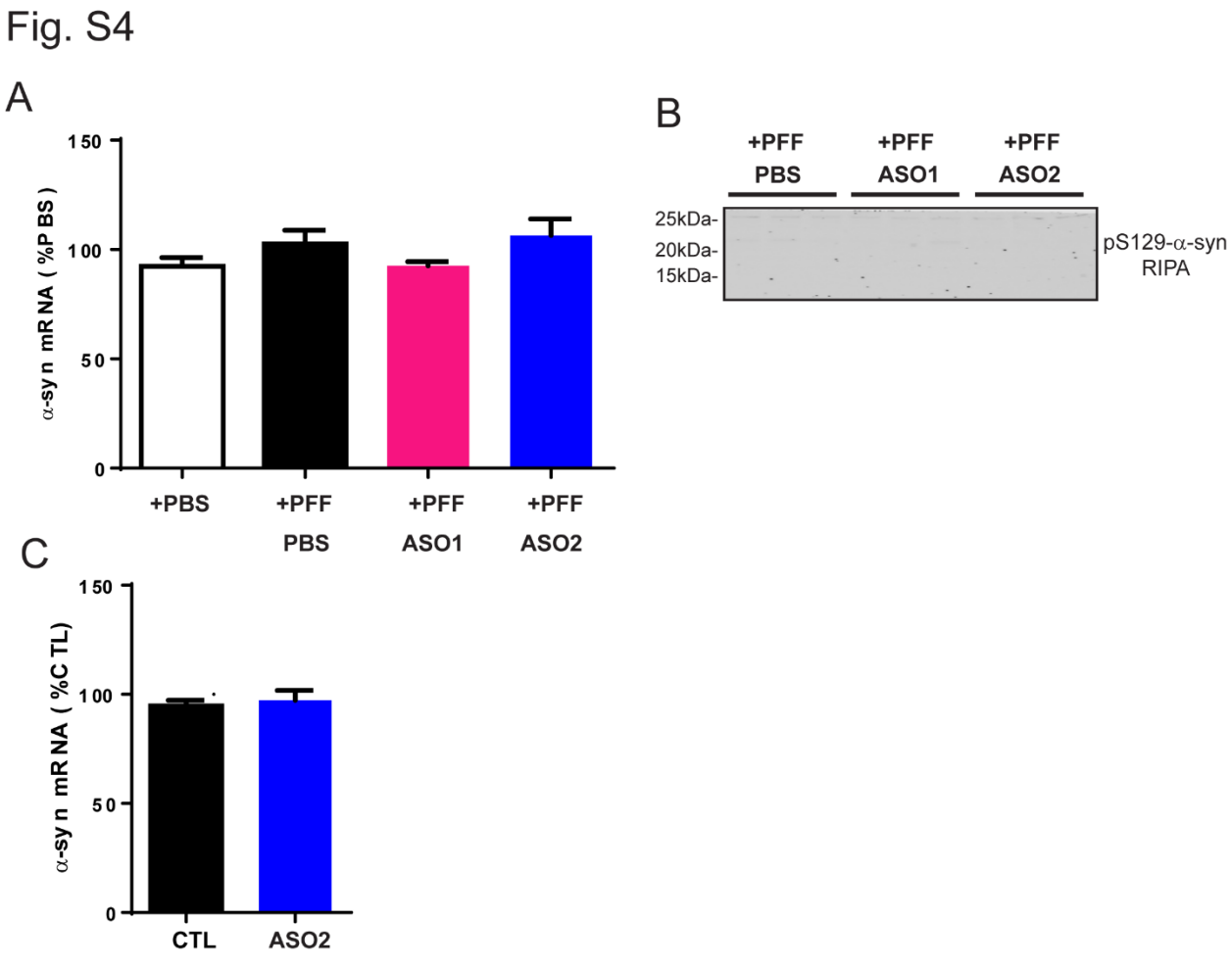

Fig. S4. No change in *SNCA* mRNA levels or RIPA-soluble pS129-α-syn in PFF-injected

mice treated with LRRK2 ASOs. A. Mice received ICVB injections of PBS, LRRK2 ASO1 (700 µg), LRRK2 ASO2 (700 µg). Fourteen days later, 5 µg of PFFs were unilaterally injected into the right striatum. Fifty-six days later, mice were sacrificed. *SNCA* mRNA was assessed in the contralateral midbrain by RT-qPCR (N=11-12). LRRK2 ASO-treated groups were compared to PBS or CTL-treated groups using one-way ANOVA with Tukey's post-test. **B.** Contralateral cortex of PFF injected mice treated with PBS, ASO1 or ASO2 were extracted in RIPA buffer and western blotted with pS129-α-syn for pathological α-syn (N=3 per group). **C.** Mice received ICVB injections of CTL ASO (700 µg) or LRRK2 ASO2 (700 µg). Fourteen days later, 5 µg of PFFs were unilaterally injected into the striatum. Ninety days later, mice received additional ICVB injections of CTL ASO (700 µg) or LRRK2 ASO2 (700 µg). The mice were sacrificed 180 days after the first ASO injection. *SNCA* mRNA was assessed in the midbrain RT-qPCR (N=6). LRRK2 ASO-treated group was compared to CTL group using student's t-test.