



Evaluation of ALN-TTR on transthyretin tissue deposition in a FAP V30M animal model

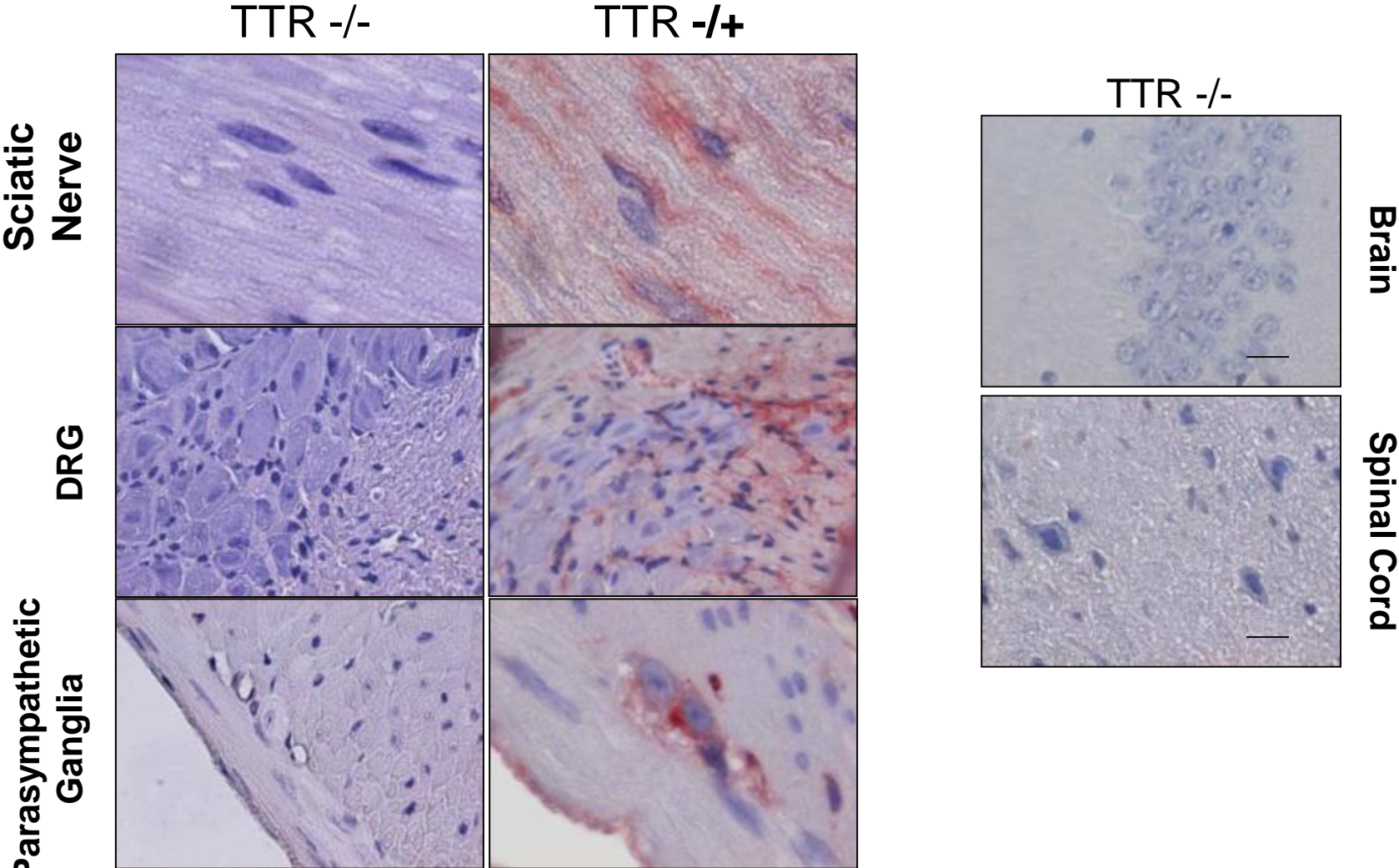
The Molecular Neurobiology
Group at IBMC – Amyloid Lab
Anylam Pharmaceuticals

ALN-TTR and SNALP (Control) Intravascular Injections in TTR V30M Mice

Strain	# animals	Age at sac.	Injected	Treatment
HSF (+/-) V30M	17	22 months	ALN-TTR (10) SNALP (7)	8 weeks I.V. biweekly
HSF (+/-) V30M	15	22 months	ALN-TTR (9) SNALP (6)	12 weeks I.V. biweekly

hTTR/HSF1-KO Mice

TTR Deposition in the PNS

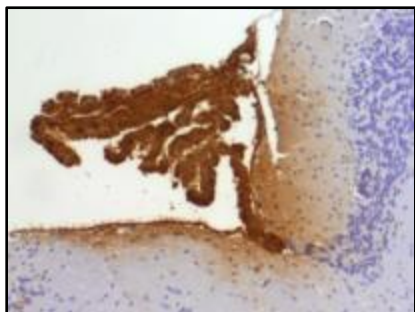


Immunohistochemistry for Human TTR

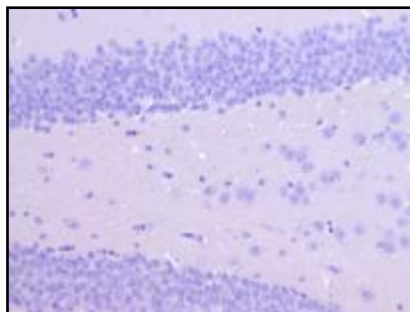
8 or 12 Weeks Treatment

ALN-TTR or control

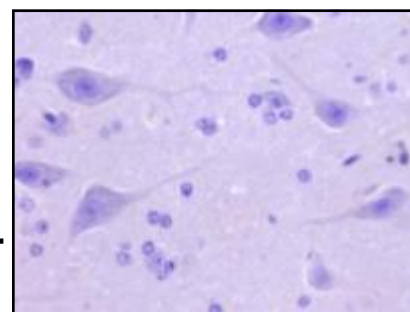
Coroid Plexus



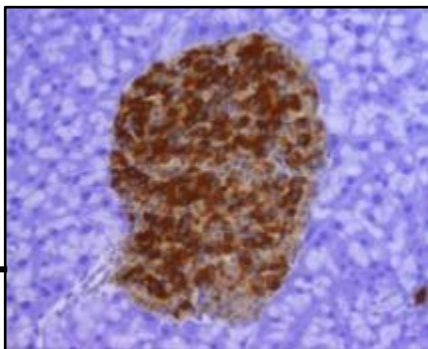
Brain



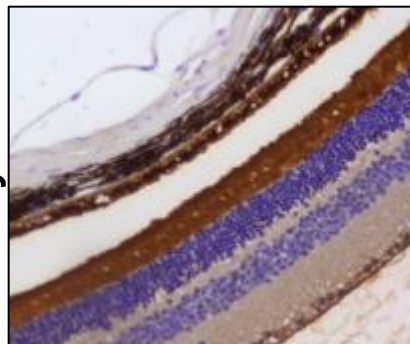
Spinal Cord



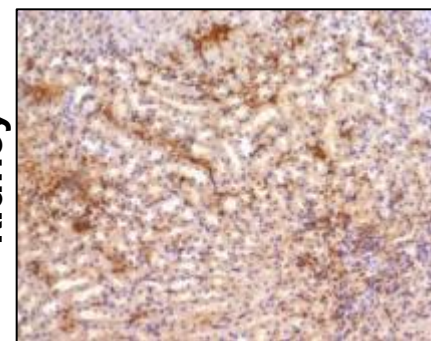
pancreas



eye



kidney



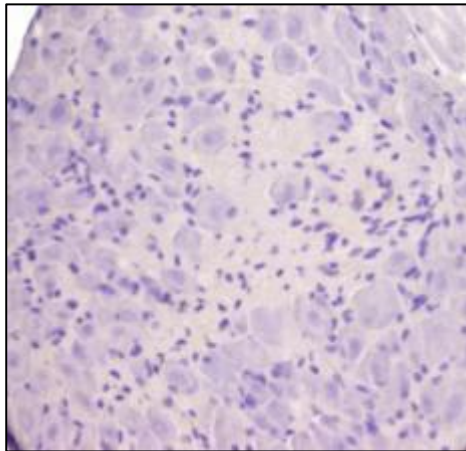
Immunohistochemistry for Human TTR

8 or 12 Weeks Treatment

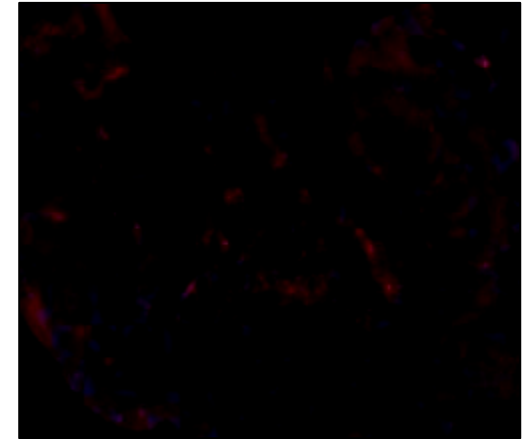
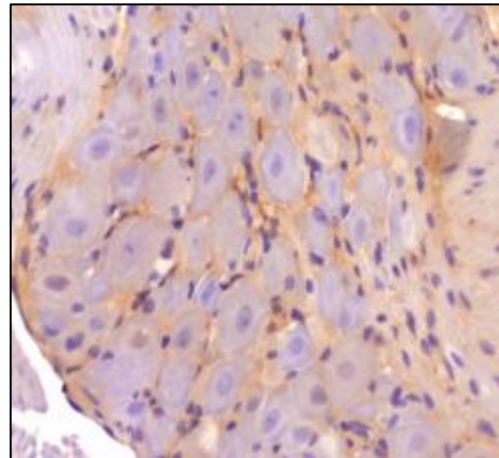
PNS: ALN-TTR vs control

DRG

ALN-TTR



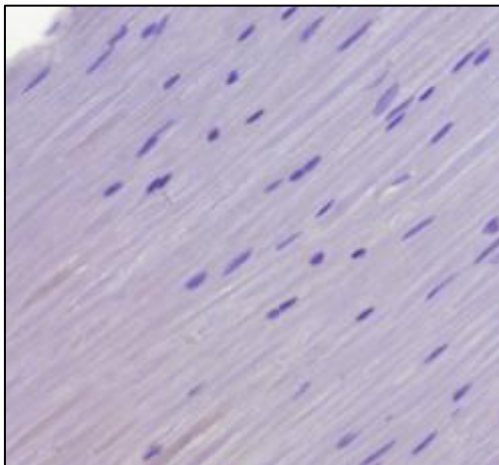
Control



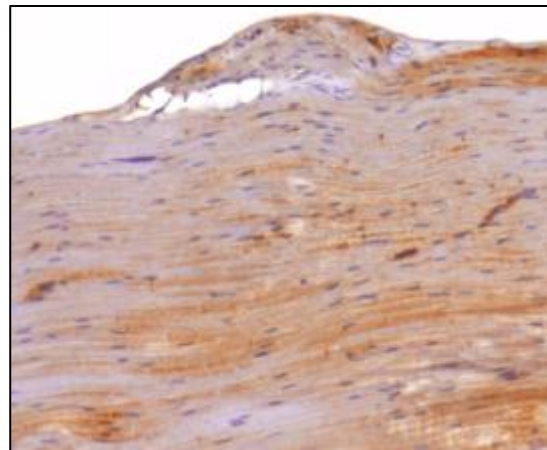
Albumin staining

Nerve

ALN-TTR



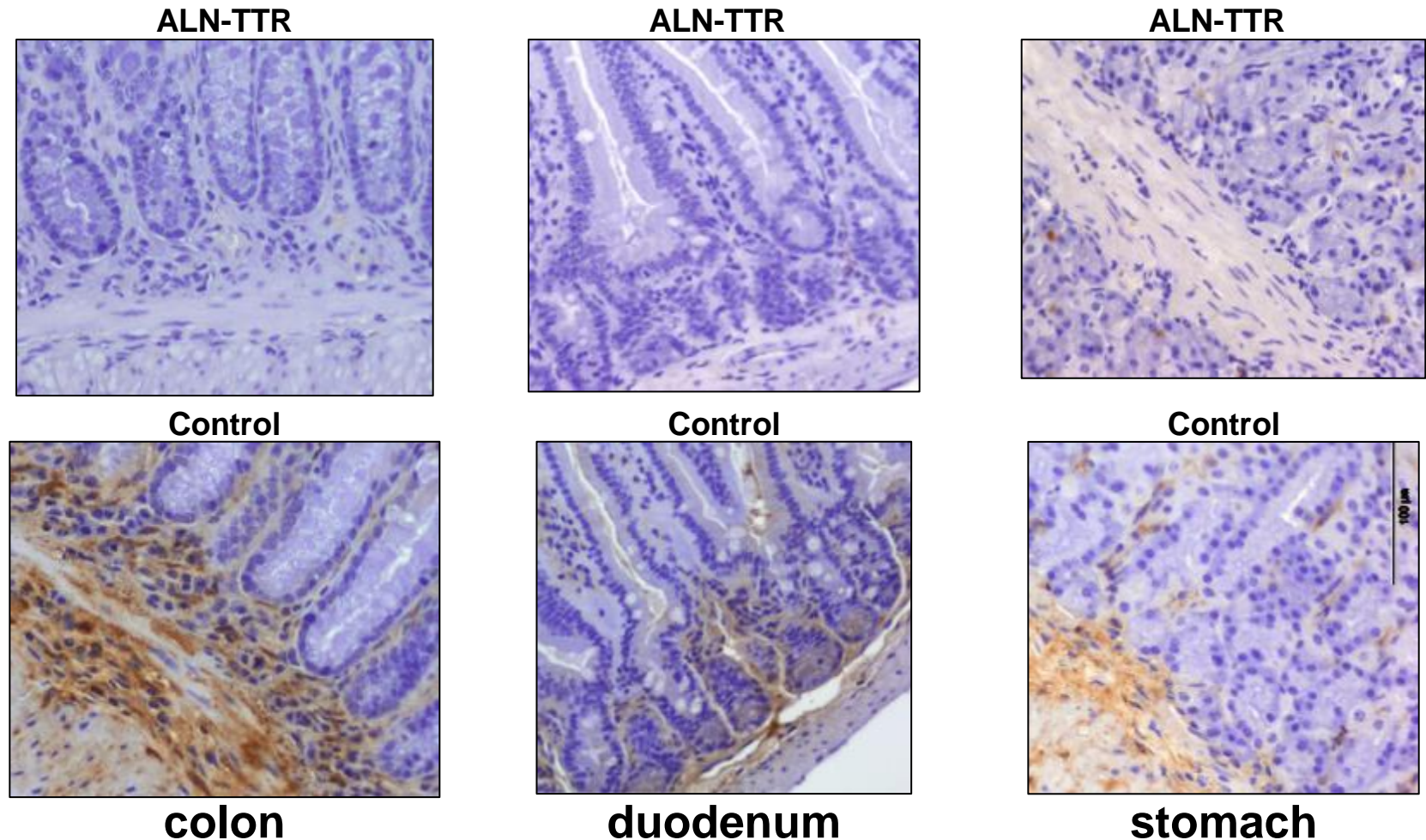
Control



Immunohistochemistry for Human TTR

8 or 12 Weeks Treatment

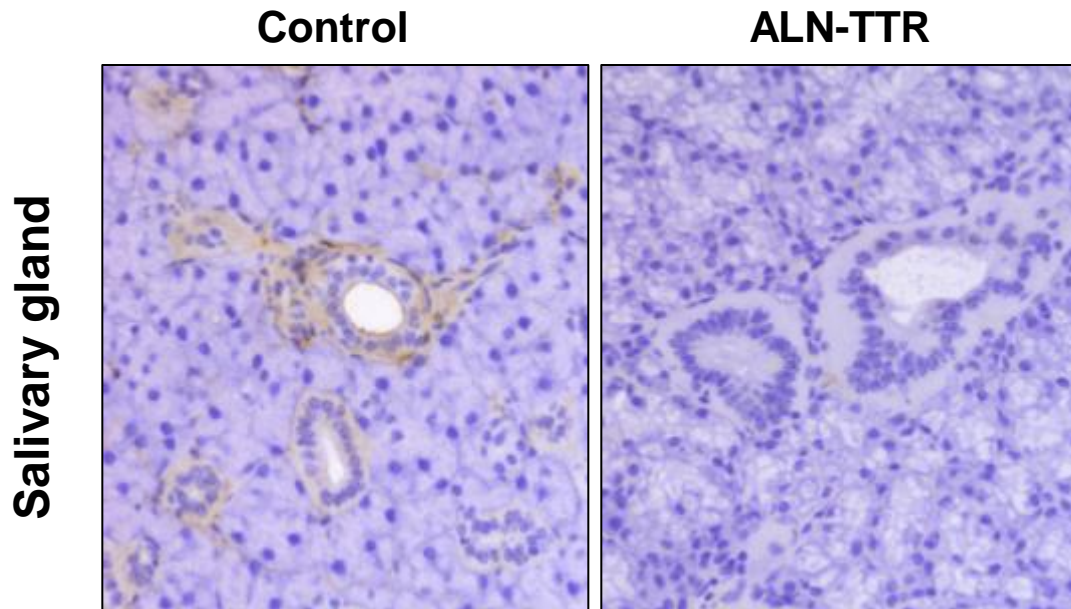
GI tract: ALN-TTR vs control



Immunohistochemistry for Human TTR

8 or 12 Weeks Treatment

GI tract: ALN-TTR vs control

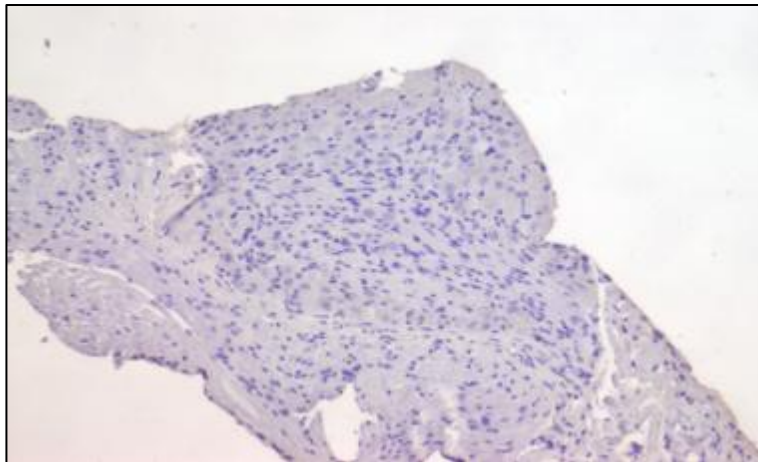


Immunohistochemistry for Macrophages

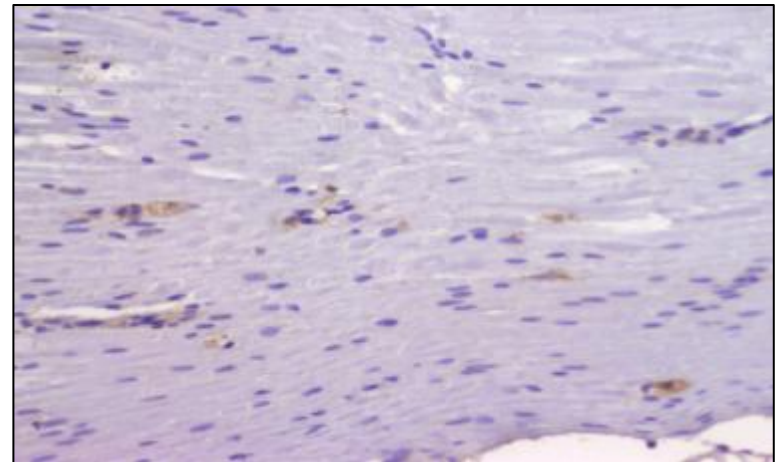
8 or 12 Weeks Treatment

No invasion

ALN-TTR (10X)



ALN-TTR (40X)

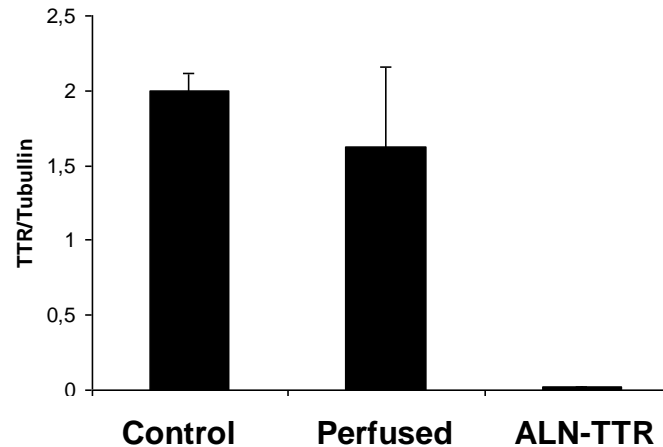
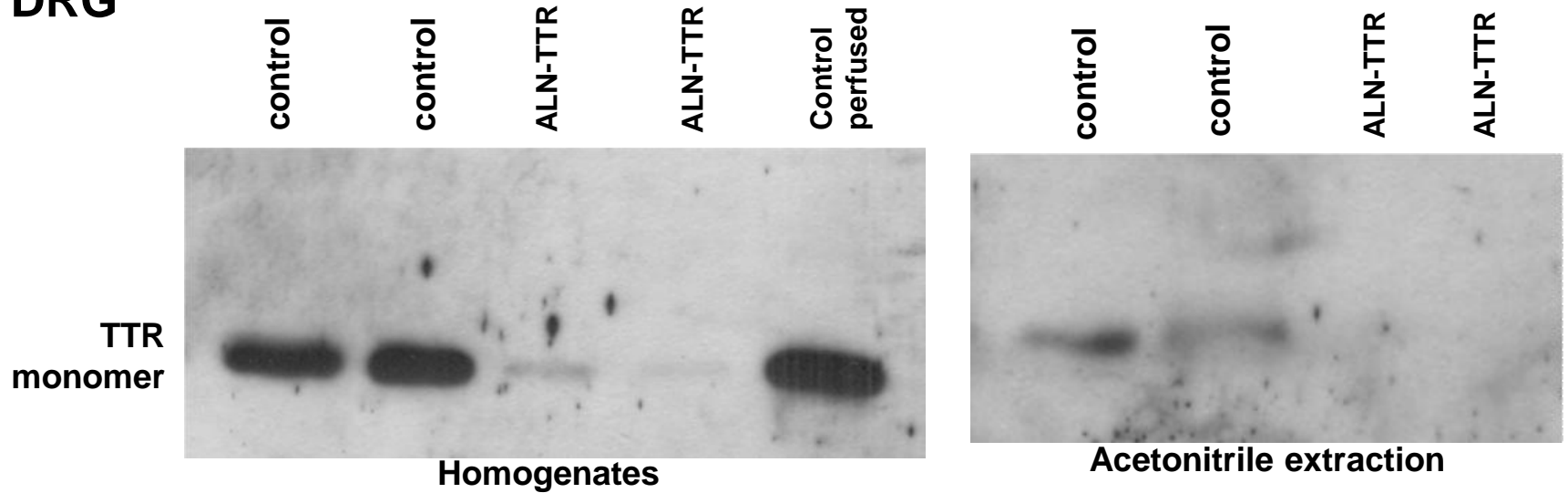


Staining IBA-1 Nerve / DRG

Western Blot for TTR

8 or 12 Weeks Treatment

DRG



Conclusions

- We have previously demonstrated the ability of ALN-TTR when administered to hTTR V30M transgenic mice to reduce both liver mRNA and serum TTR levels > 90% as compared to control siRNAs
- ALN-TTR, when administered to hTTR V30M transgenic mice, leads to regression (old mice) of pre-existing TTR deposits in key target tissues, including: dorsal root ganglia, sciatic nerve, stomach, and intestines
- Regression of TTR protein was confirmed by western blot and acetonitrile tissue extraction
- ALN-TTR has no effect on the expression of TTR in other tissues, including the choroid plexus, eye, kidney, and pancreas
- The mechanism of regression of TTR following administration of ALN-TTR are currently being investigated
- These findings demonstrate the potential therapeutic benefit of an RNAi therapeutic targeting TTR for the treatment of TTR-mediated amyloidosis (ATTR)



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