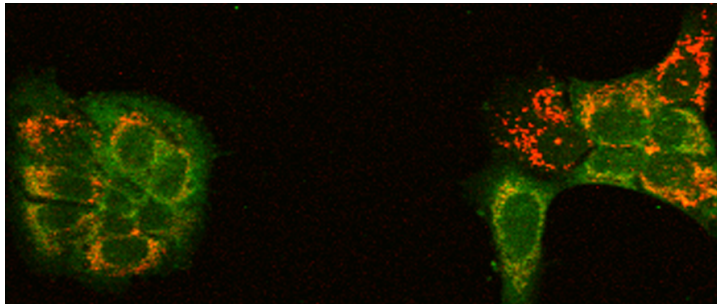
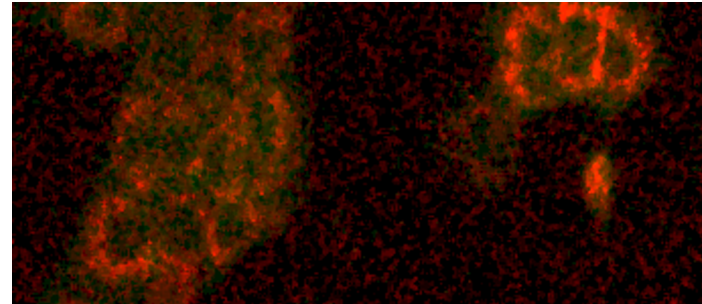


AAV9-ApaLI



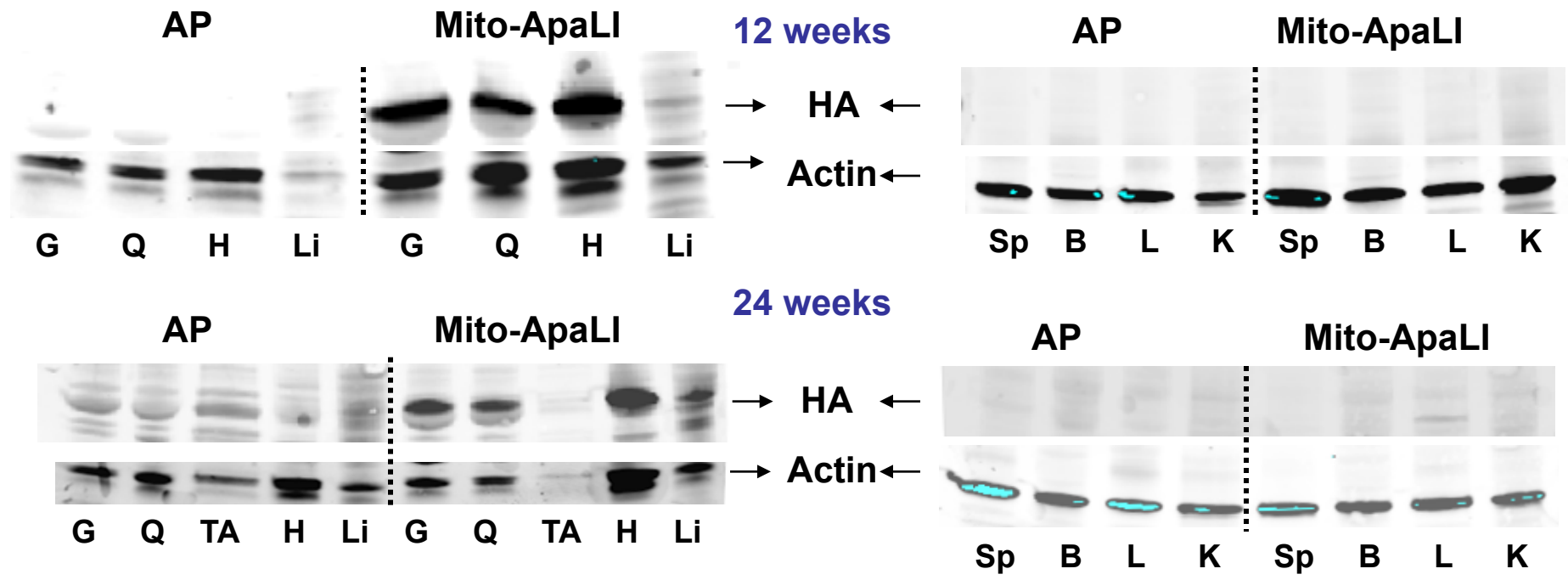
AAV9-AP



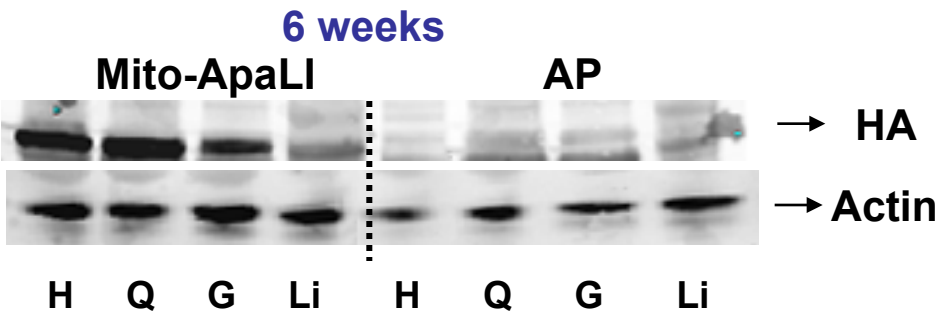
### **S.1. Expression of AAV9[Mito-ApaLI-HA] in cultured cells**

The mitochondrial localization of ApaLI was confirmed by confocal microscopy of mouse cell line (hepatocyte-derived) infected with AAV9[Mito-ApaLI-HA] (1,000vg/cell). Co-localization of Mito-ApaLI-HA (green) and Mitotracker (red) was evident in transduced cells after 10 days of culture. No expression was observed in the control AAV9[AP].

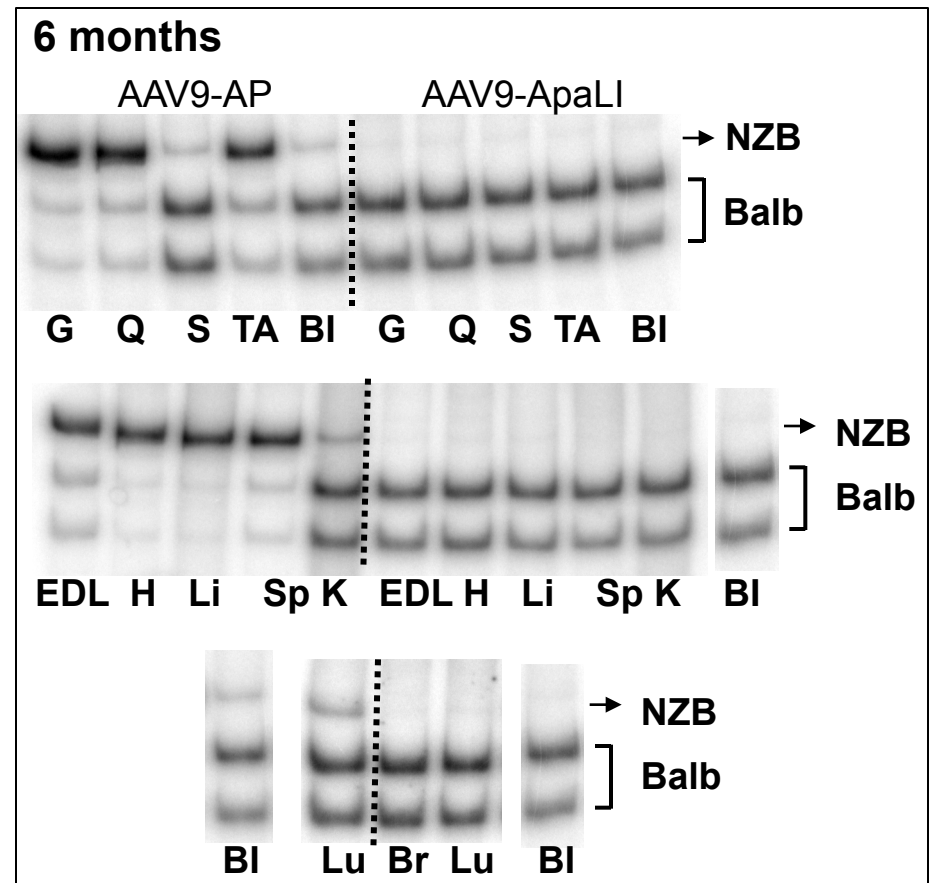
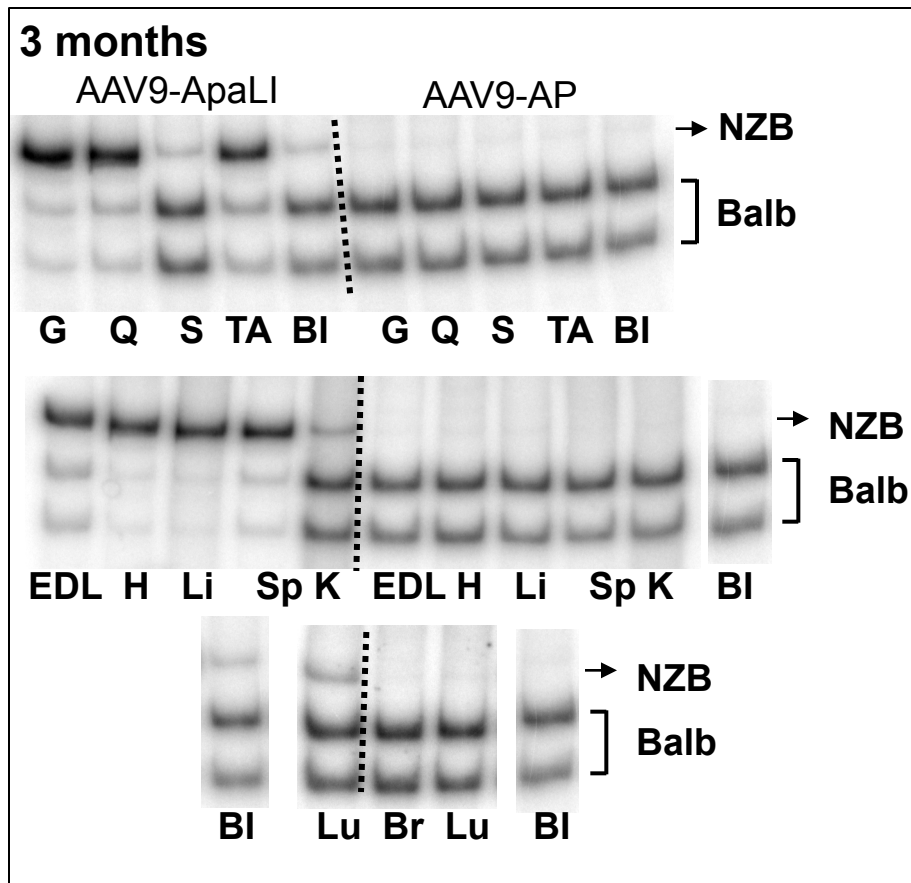
### A AAV9-ApaLI expression after IP Injection



### B AAV9-ApaLI expression after Temporal-Injection



**S2. Long term expression of AAV9-ApaLI. A.** The figure shows western blotting 12 and 24 weeks after IP injection in neonates ( $5 \times 10^{11}$ vg/mouse), with high expression detected in all skeletal muscles, including gastrocnemius (G), quadriceps (Q), and heart (H). No expression was observed in spleen (Sp), brain (B), lung (L) and kidney (K), with low expression in liver (L). Actin was used as loading control. The animal injected with the control (AAV9[AP]) showed no HA expression **B.** Expression in different tissues was also evaluated by western blotting at 6 weeks post delivery of the transgene through temporal vein injection showing high expression in heart (H), quadriceps (Q), and gastrocnemius (G), with less expression in liver (L). Actin was used as loading control.



**S3. AAV9[mito-ApaLI-HA] induces long term shift in mtDNA heteroplasmy in targeted tissues after IP injection of the transgene.** NZB mtDNA genotype was quantified by the last-cycle hot PCR/RFLP analysis (as described in materials and methods). DNA samples from injected animals with AAV9[AP] or AAV9[mito-ApaLI-HA] were evaluated for the increase of NZB mtDNA after 3 and 6 months after IP delivery of the transgenes. Significant increase of the NZB mtDNA was observed after injection of AAV9[mito-ApaLI-HA] in gastrocnemius (G), quadriceps (Q), soleus (S), tibialis anterior (TA), EDL, and heart (H). No change was observed in spleen (Sp), brain (B), lung (L) and kidney (K), with a small change in liver (L). BI: Before Injection DNA samples obtained from ears. U: Uncut DNA.