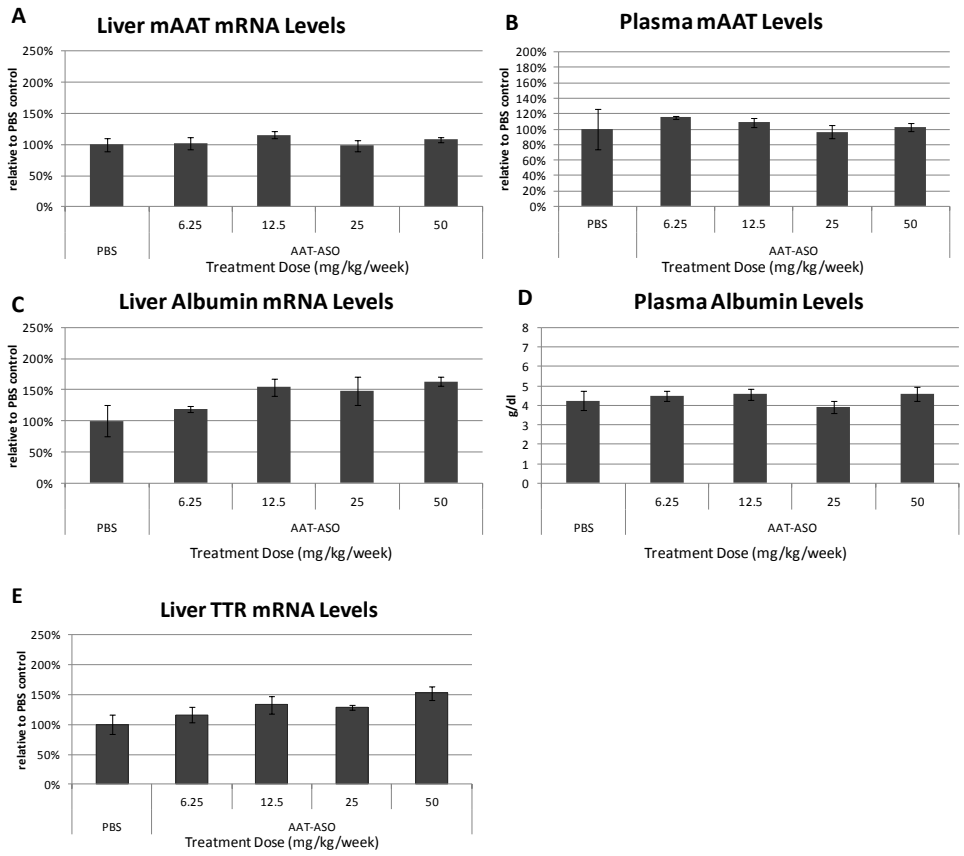
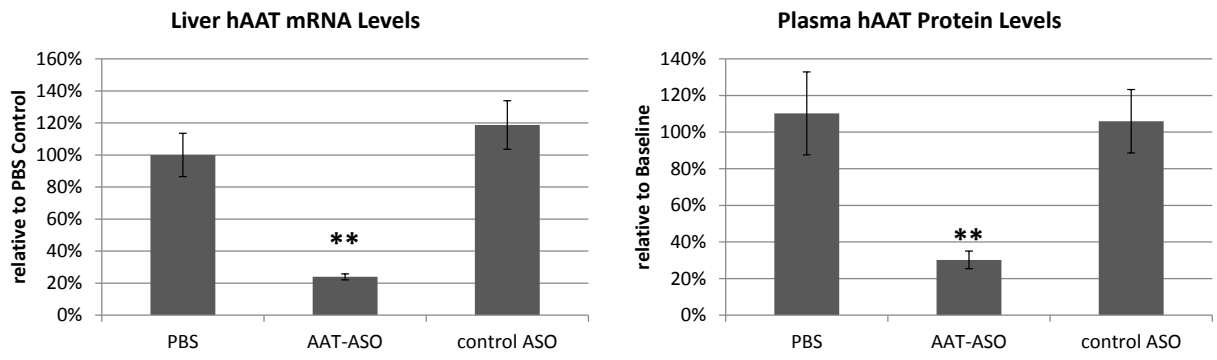
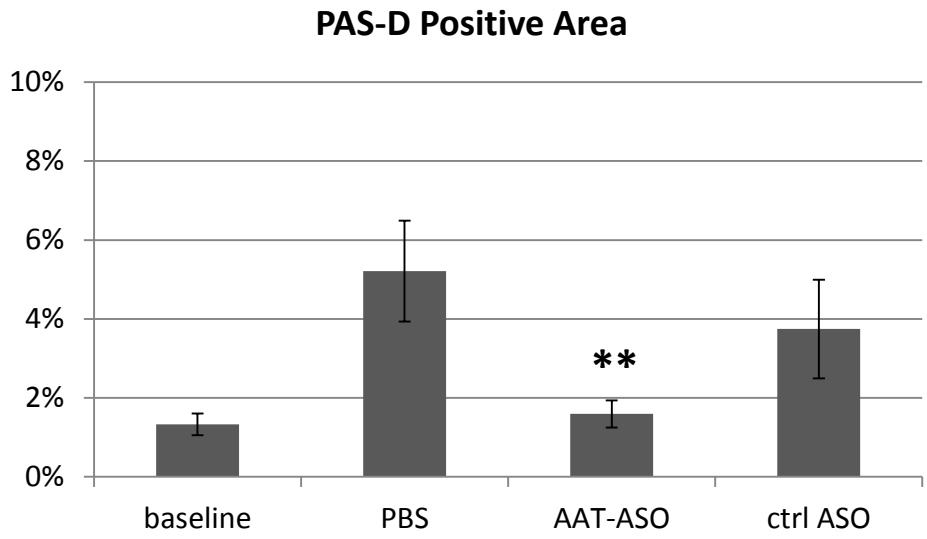


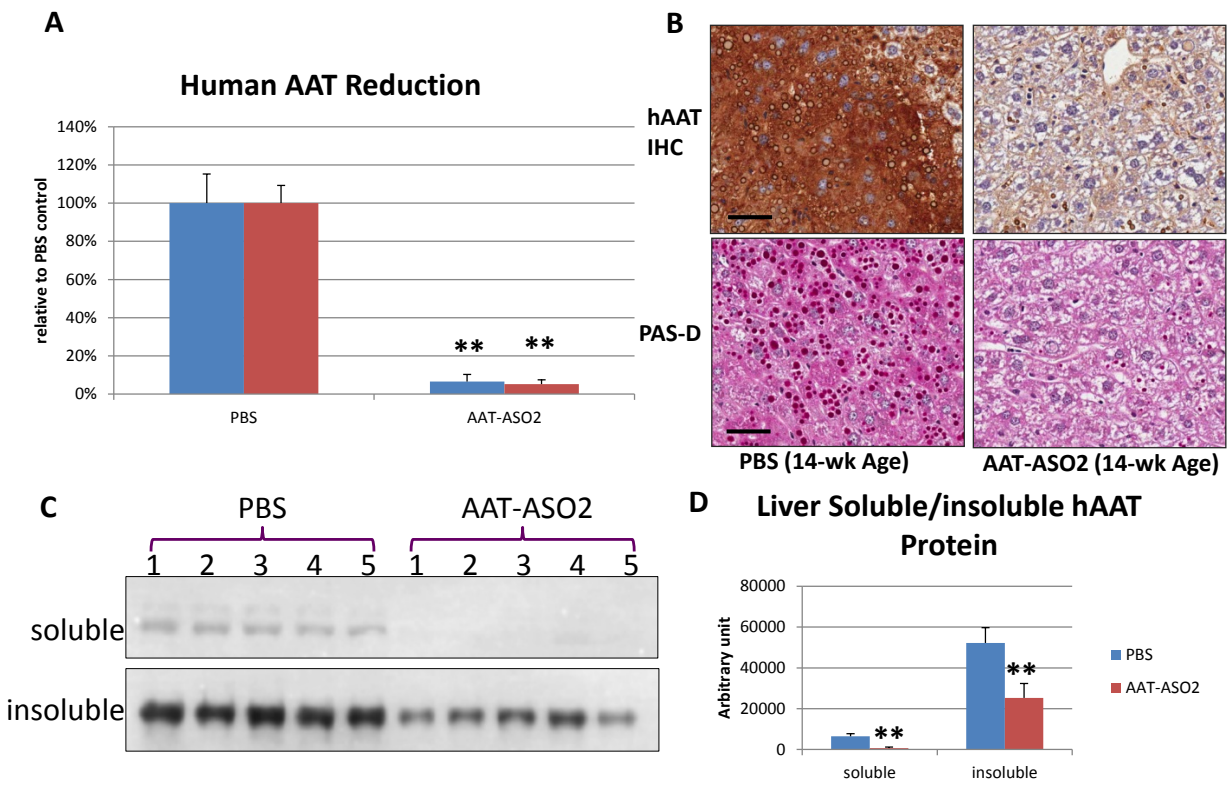
Supplementary Figure 1. No dramatic changes in mouse AAT or hepatic genes after human specific AAT-ASO treatment in PiZ mice. (A) Mouse liver *AAT* mRNA levels, (B) Plasma mouse AAT protein levels, (C) Liver albumin mRNA levels, (D) Plasma albumin protein levels and (E) Liver transthyretin mRNA levels were measured in PiZ mice after AAT-ASO treatment. Six-week- old PiZ mice were treated for 4 weeks with the indicated doses of AAT-ASO via subcutaneous injection. Liver mRNA levels were quantified by qRT-PCR (TaqMan), mouse AAT was determined by ELISA (Alpco), and plasma albumin levels were determined by clinical chemistry analyzer. Results represent mean ± standard deviation (N=4).



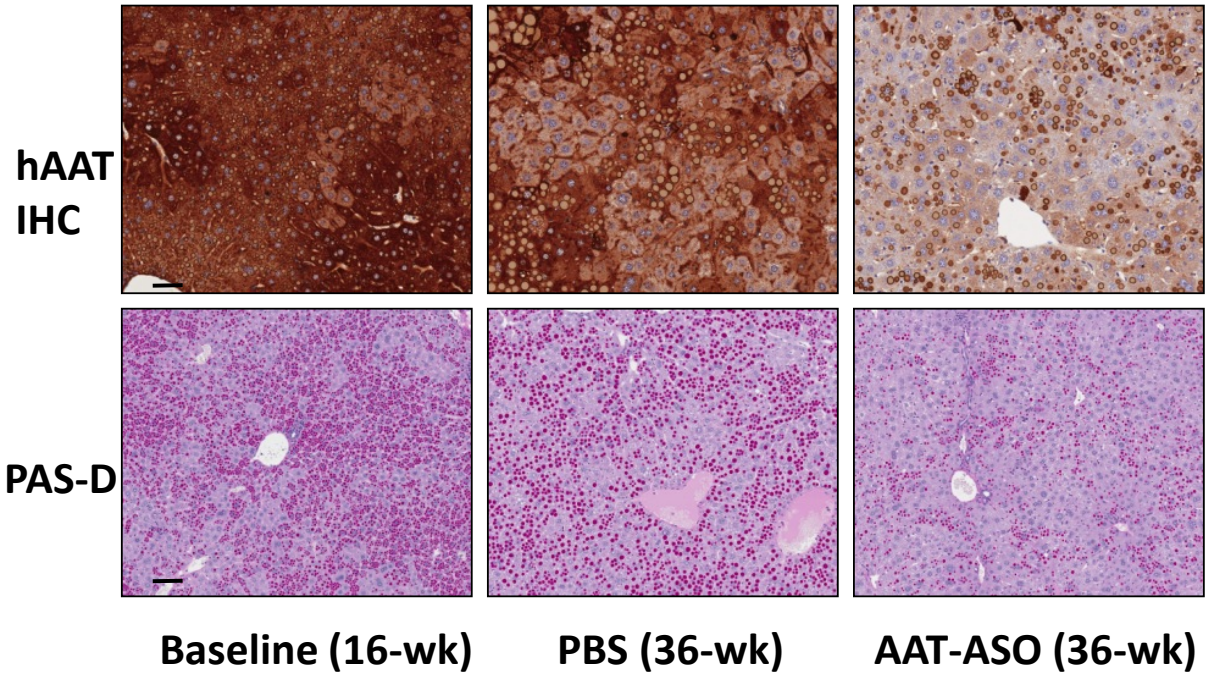
Supplementary Figure 2. A scrambled control ASO did not affect *hAAT* expression in PiZ mice. (A) Liver *hAAT* mRNA levels. (B) Plasma hAAT protein levels. Six-week-old PiZ mice were treated with PBS, AAT-ASO or control ASO for 6 weeks. Results represent mean ± standard deviation (N=4). **: P<0.01 by 1-way ANOVA with Tukey's comparisons.



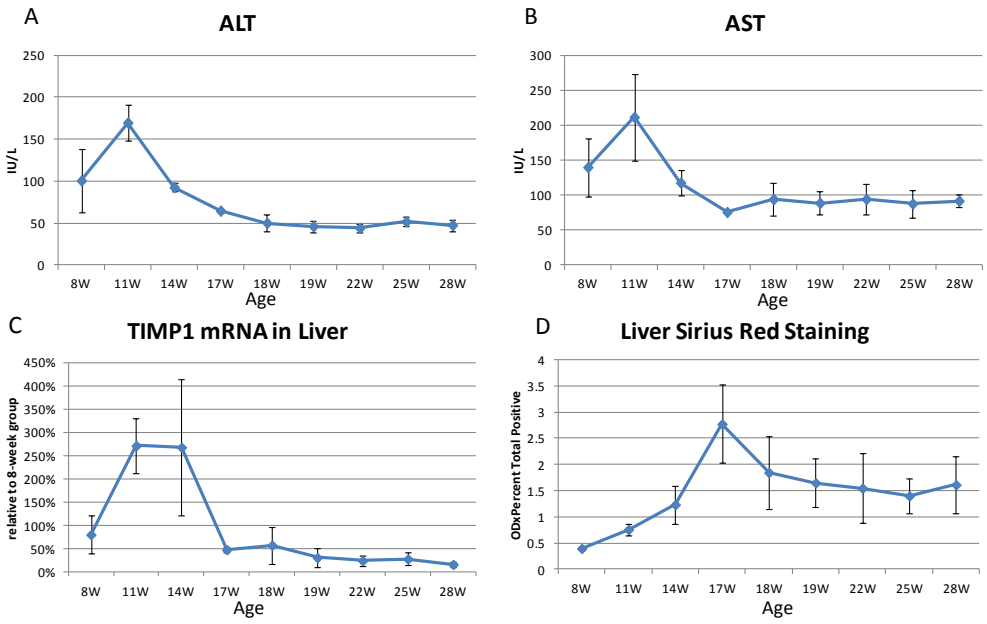
Supplementary Figure 3. Quantitation of PAS-D staining shown in Figure 2B. Six-week-old PiZ mice were treated for 8 weeks with 50 mg/kg/week AAT-ASO or control ASO (ctrl ASO) via subcutaneous injection. PAS-D positive area was quantitated with Aperio software. Results represent mean ± standard deviation (N=6 per group). **: $P<0.01$ by 1-way ANOVA with Tukey's comparisons when AAT-ASO treatment group was compared with PBS or control ASO treatment group. No significant difference was observed between PBS group and control ASO treatment group ($P>0.05$) nor baseline and AAT-ASO treatment group ($P>0.05$).



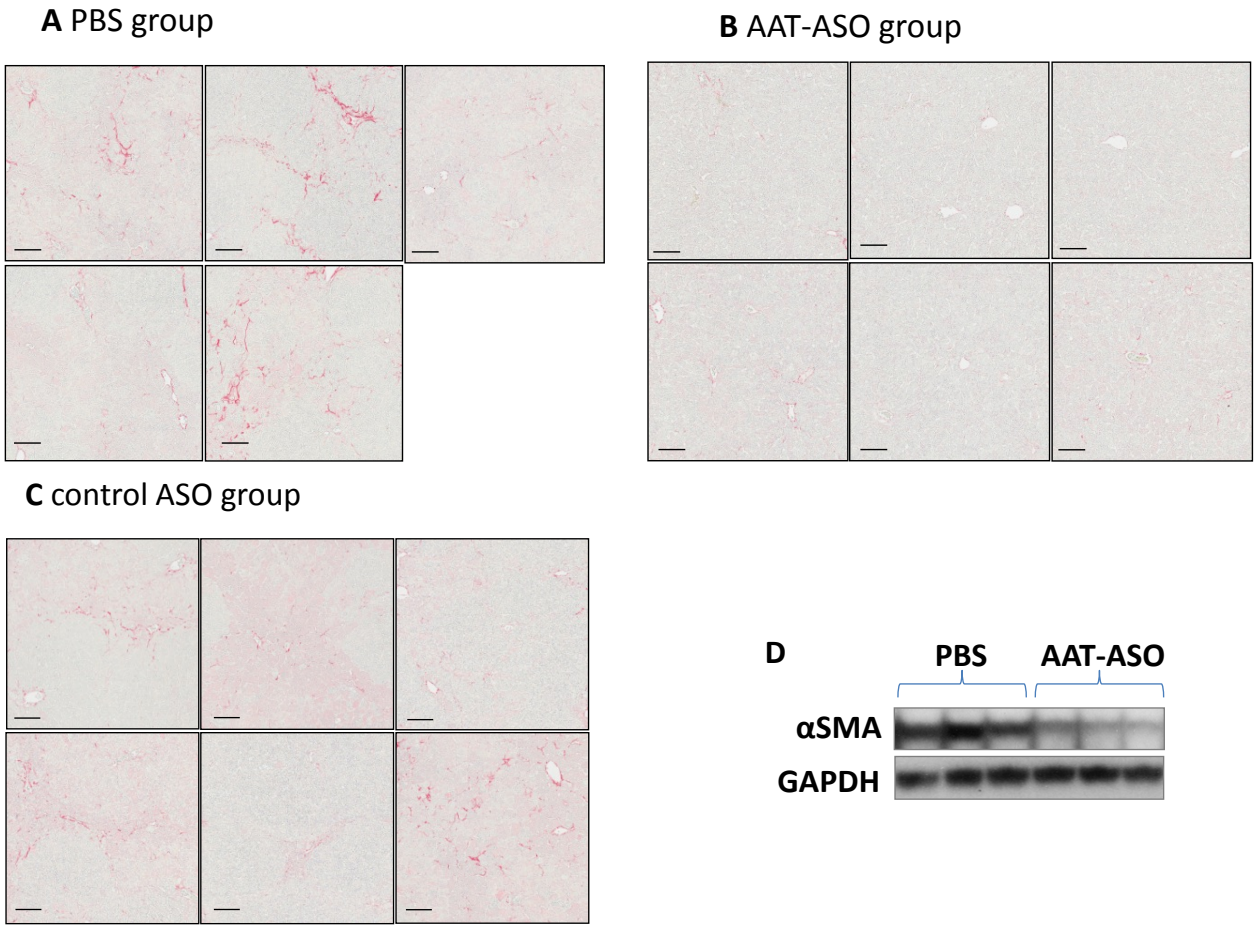
Supplementary Figure 4. A second *hAAT* specific ASO (AAT-ASO2) reduced *hAAT* expression and globule formation in PiZ mice. (A) Six-week-old PiZ mice were treated for 8 weeks with 50 mg/kg/week AAT-ASO2 via subcutaneous injection. *hAAT* mRNA levels in liver were quantified by qRT-PCR (TaqMan) and plasma AAT protein levels were determined by clinical chemistry analyzer. (B) Top panel: Immunohistochemistry (IHC) staining for AAT protein in liver. Bottom panel: Periodic acid-Schiff staining with diastase treatment (PAS-D) in liver. Scale bar: 50μm. (C) Soluble and aggregate fractions from PiZ liver were analyzed by western blot analysis with an anti-human AAT antibody. (D) Quantitation of western blot data shown in Figure 2C. Results represent mean ± standard deviation (N=5 for treatment groups); **: P<0.01 by Student's t-test.



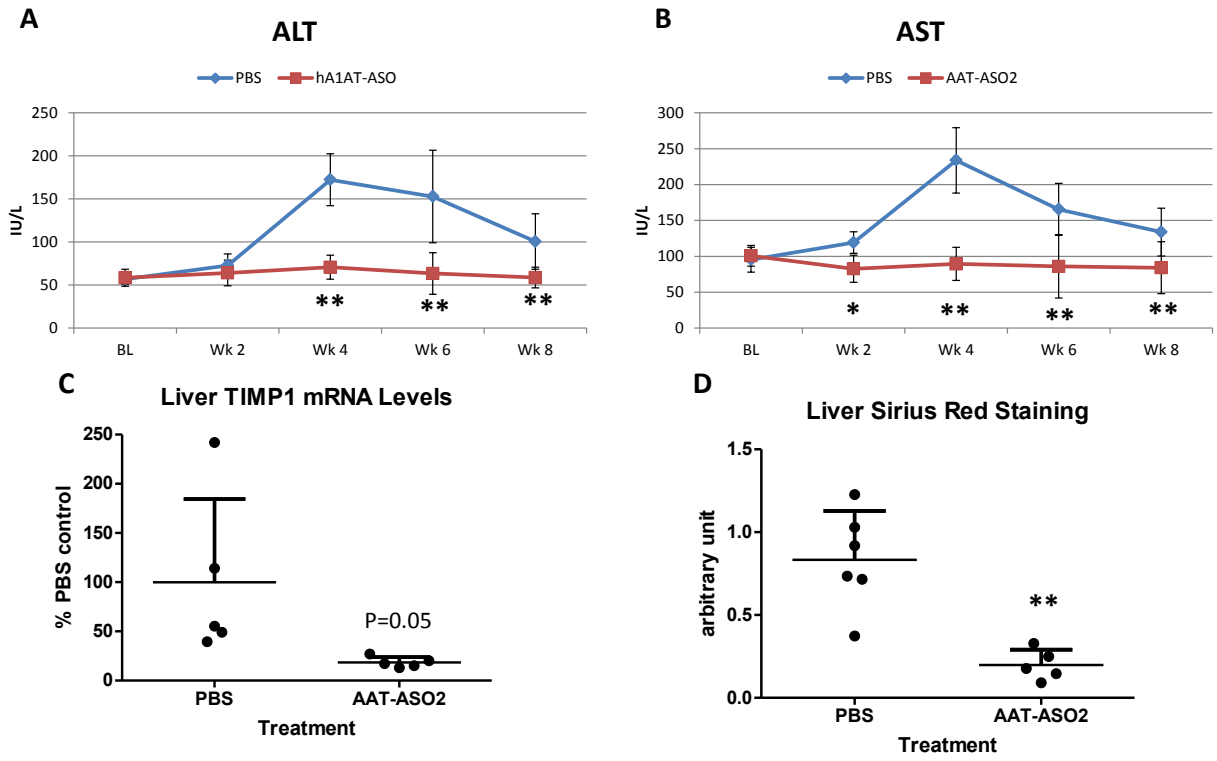
Supplementary Figure 5. AAT-ASO treatment reversed liver globule accumulation and reduced hAAT in hepatocytes in PiZ mice. Sixteen-week-old PiZ mice were treated for 20 weeks with 50 mg/kg/week AAT-ASO via subcutaneous injection. Top panel: Immunohistochemistry (IHC) staining for AAT protein in liver. Bottom panel: Periodic acid-Schiff staining with diastase treatment (PAS-D) in liver. Scale bar: 50μm.



Supplementary Figure 6. Longitudinal analysis of PiZZ mice of different age. (A) Plasma ALT levels. (B) Plasma AST levels. (C) Liver TIMP1 mRNA levels determined by qRT-PCR. (D) Quantitation of Sirius red staining in PiZZ liver.



Supplementary Figure 7. AAT-ASO treatment significantly reduced fibrosis in PiZZ mice. Five-week-old PiZZ mice were treated for 11 weeks with AAT-ASO via subcutaneous injection. (A) Liver Sirius red staining for individual animals in PBS treatment group (N=5 per group). (B) Liver Sirius red staining for individual animals in AAT-ASO treatment group (N=6). (C) Liver Sirius red staining for individual animals in control ASO treatment group (N=6). (D) Western blot of liver α-SMA in PBS or AAT-ASO treatment groups.



Supplementary Figure 8. A second *hAAT*-specific ASO (AAT-ASO2) reduced liver fibrosis in PiZZ mice. Eight-week-old PiZZ mice were treated for 8 weeks with AAT-ASO2 via subcutaneous injection. (A) Plasma ALT levels and (B) plasma AST levels were monitored throughout the treatment period. Significant reduction of (C) liver TIMP1 expression and (D) Sirius red staining were observed after AAT-ASO2 treatment. Results represent mean ± standard deviation (N=5); *: P<0.05, **: P<0.01 by repeated measures 2-way ANOVA for panels A-B and Student's t-test for panels C-D.

Supplementary Table 1 Additional primer probe set sequences

Name	Forward Sequence	Reverse Sequence	Probe Sequence
mAAT	TTCTGGCAGGCCTGTGTTG	ATCCTTCTGGGAGGTGTCTGTCT	CCCCAGCTTTCTGGCTGAGGATGTTC
mTTR	CGTACTGGAAGACACTTGGCATT	GAGTCGTTGGCTGTGAAAACC	CCCGTTCCATGAATTCGCGGATG
mAlbumin	TGAAGAAAGCCCACTGTCTTAGTG	TTCCTGGTCCTCAACAAAATCAG	TGACACCATGCCTGCTGATCTGCC