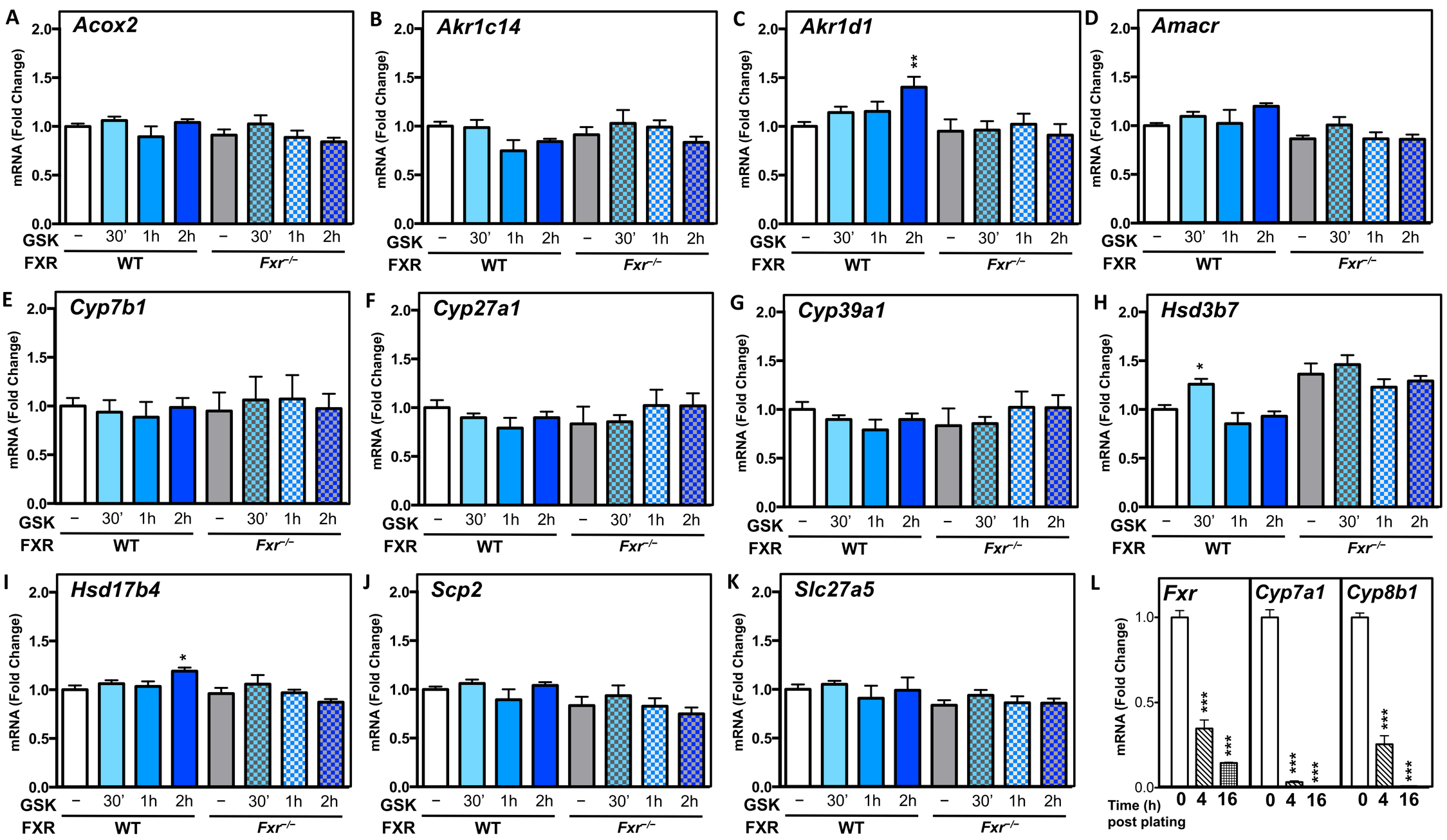
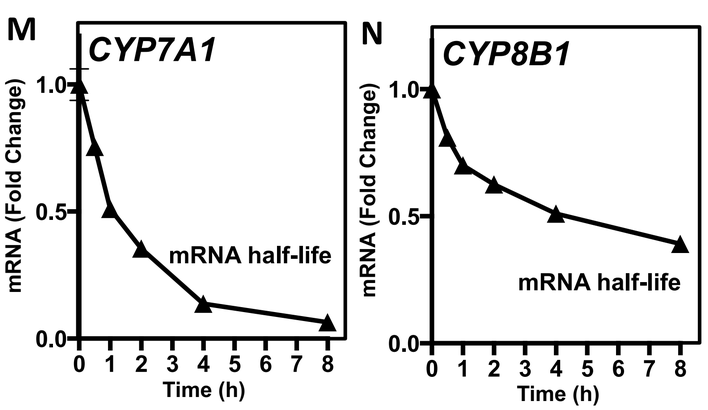
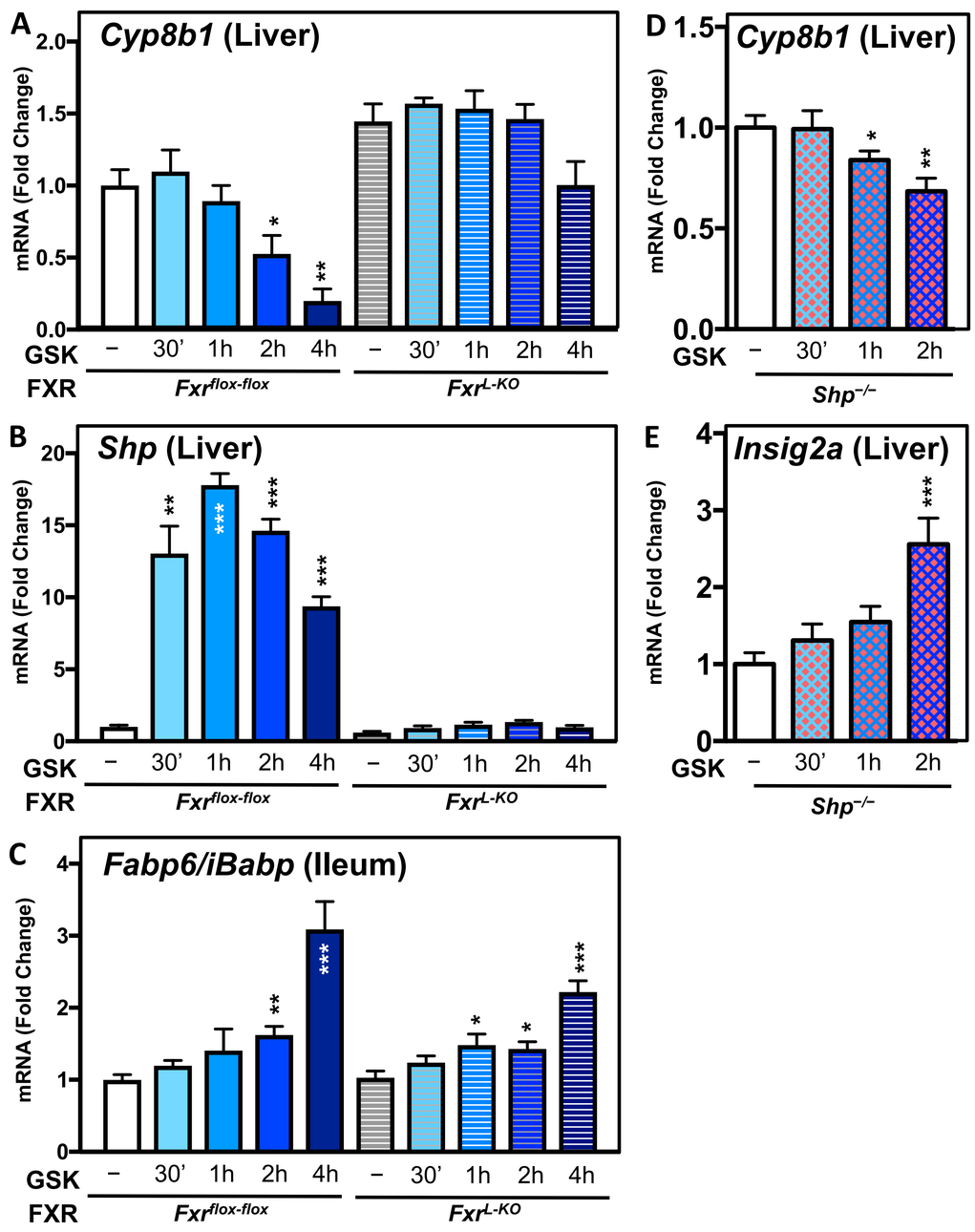


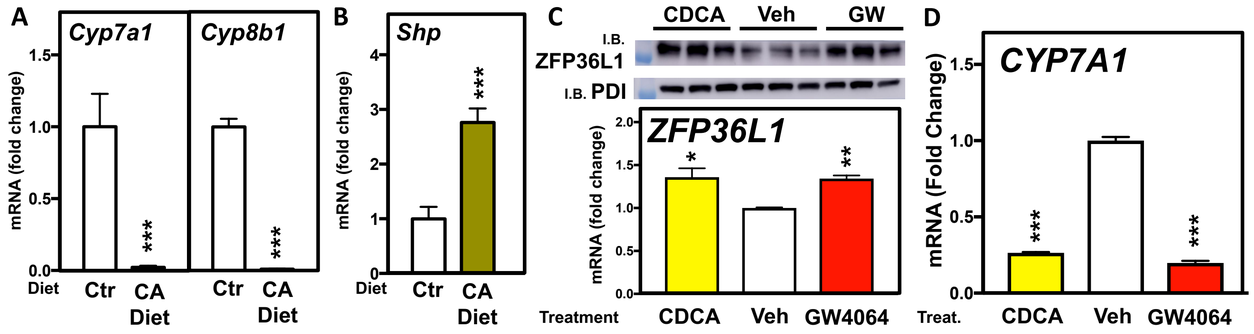


Supplementary Figure 1 – FXR activation leads to rapid changes in gene expression
(A-K) Hepatic gene expression of bile acid synthesis genes from wild-type and *Fxr*$^{-/-}$ mice. Mice were treated with either vehicle (WT n=16; *Fxr*$^{-/-}$ n=7) or GSK2324 and RNA isolated after 30 minutes (WT n=12; *Fxr*$^{-/-}$ n=6), 1h (WT n=10; *Fxr*$^{-/-}$ n=6) or 2h (WT n=8; *Fxr*$^{-/-}$ n=7). Gene expression analysis was determined by RT-qPCR and normalized to *Tbp*. (L) Gene expression of *Cyp7a1*, *Cyp8b1*, and *Fxr* from primary hepatocytes that were freshly isolated (t=0) or the same hepatocytes plated for 4 or 16 hours on collagen coated plates (n=6 wells/condition). (M,N) *CYP7A1* and *CYP8B1* mRNA levels in IHH cells treated with actinomycin D for various time points. Gene expression was determined by RT-qPCR and data are normalized to *36B4*. Data are normalized to *36B4*. All data shown as mean ± SEM. Asterisks indicate statistically significant differences (*p<0.05; **p<0.01; *** p<0.001) by one way ANOVA.



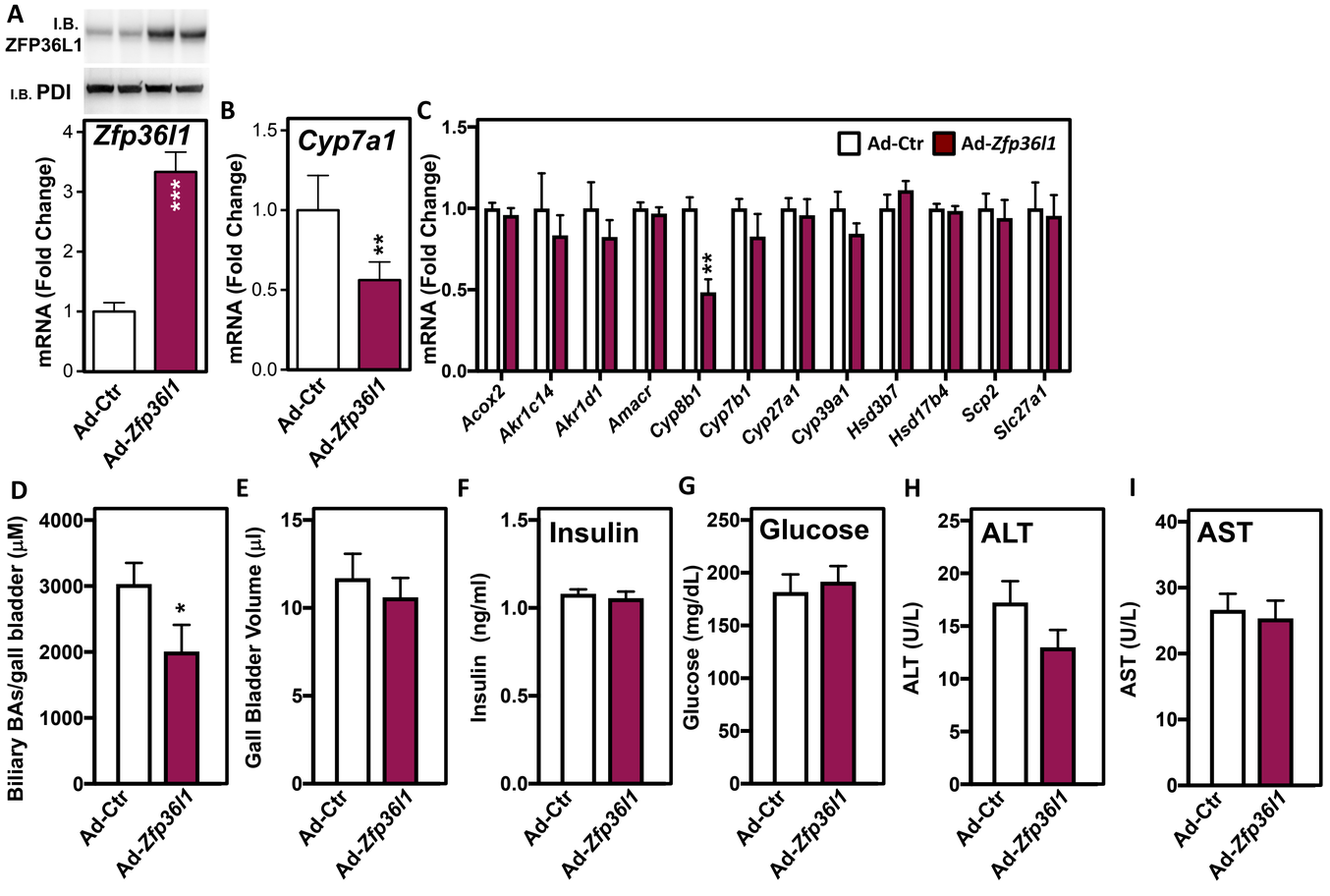
Supplementary Figure 2 – Decrease in *Cyp8b1* following FXR activation required hepatic FXR but is independent of SHP

(A-C) Gene expression of hepatic *Cyp8b1* and *Shp* and ileal *Fabp6* in littermate $Fxr^{flox\text{-}flox}$ and $Fxr^{L\text{-}KO}$ mice were treated with either vehicle (n=13 $Fxr^{flox\text{-}flox;}$ n=11 $Fxr^{L\text{-}KO}$) or GSK2324 for 30 minutes (n=9 $Fxr^{flox\text{-}flox;}$ n=8 $Fxr^{L\text{-}KO}$), 1h (n=7 $Fxr^{flox\text{-}flox;}$ n=9 $Fxr^{L\text{-}KO}$), 2h (n=8 $Fxr^{flox\text{-}flox;}$ n=7 $Fxr^{L\text{-}KO}$) or 4h (n=5 $Fxr^{flox\text{-}flox;}$ n=10 $Fxr^{L\text{-}KO}$). (D-E) Gene expression of hepatic *Cyp8b1* and *Insig2a* in $Shp^{-/-}$ mice treated with either vehicle (n=8) or GSK2324 for 30 minutes (n=8), 1h (n=7) or 2h (n=8). Gene expression analysis was determined by RT-qPCR and normalized to *Tbp*. All data shown as mean ± SEM. Asterisks indicate statistically significant differences (*p<0.05; **p<0.01; *** p<0.001) by one way ANOVA.



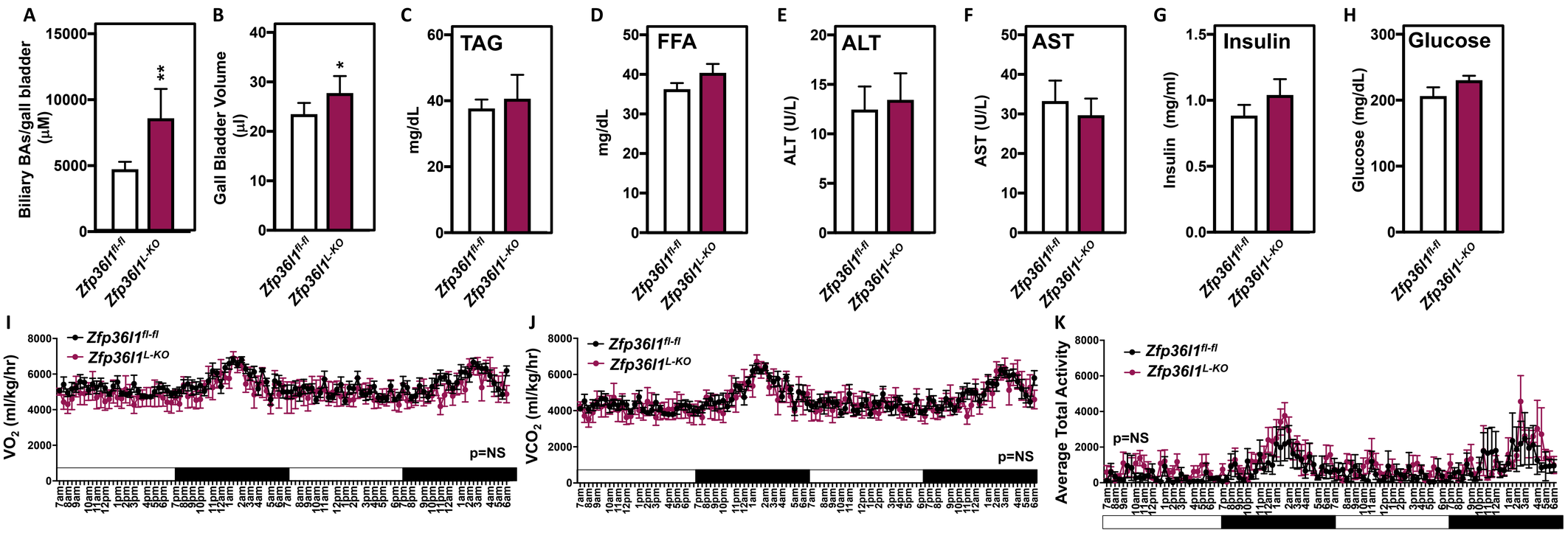
Supplementary Figure 3 – *Zfp36l1* is a direct FXR target gene

(A,B) Hepatic *Cyp7a1,Cyp8b1* and *Shp* mRNA expression in C57BL/6 wild-type fed a control diet (Ctr; n=8) or a diet supplemented with 0.5% cholic acid (CA Diet; n=8) for 7 days. Gene expression analysis was determined by RT-qPCR and normalized to *Tbp*. (C) ZFP36L1 mRNA and protein (D) *CYP7A1* mRNA in immortalized human hepatocytes (IHH) treated with either CDCA (100μM) or GW4064 (1μM) for 24h (n=3 wells/condition). (E) *ZFP36L1* mRNA levels were measured in IHH cells treated with actinomycin D for the indicated times (n=6 wells condition). (F and G) *ZFP36L1* mRNA levels in IHH cells treated with either CDCA (100μM) or GW4064 (1μM) for 30', 1h and 2h (n=4 wells/condition). Gene expression data was normalized to *36B4* or *TBP*. All data shown as mean ± SEM. Asterisks indicate statistically significant differences (*p<0.05; **p<0.01; *** p<0.001) by Student's *t*-test for A-D and one-way ANOVA for F-G.

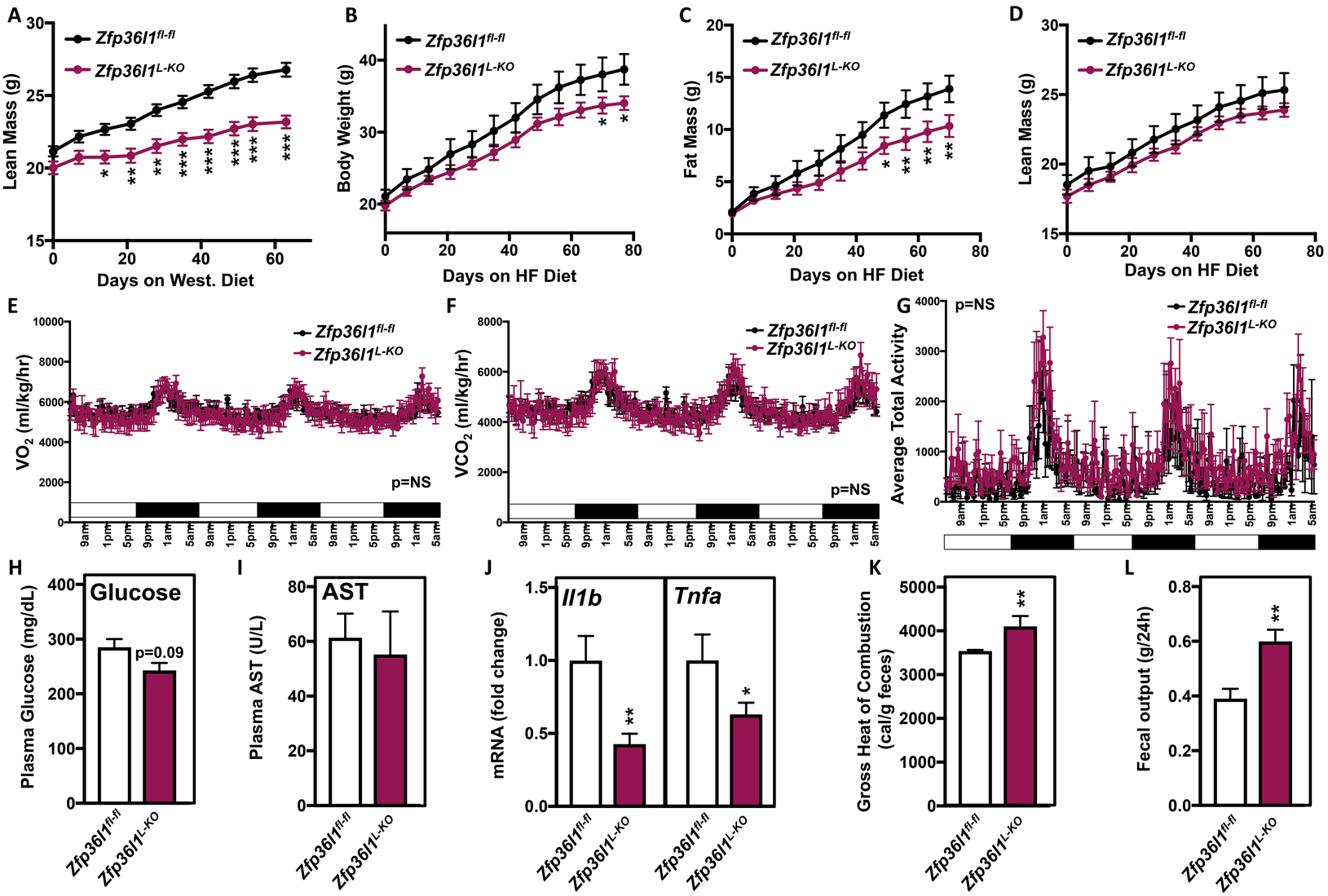


Supplementary Figure 4 – ZFP36L1 gain-of-function decreases CYP7A1 and alters bile acids *in vivo*

(A) *Zfp36l1* mRNA and protein and (B) *Cyp7a1* and (C) other bile acid synthesis genes in female C57BL/6 wild-type mice treated with either Ad-control (Ad-Ctr) or Ad-*Zfp36l1* for 5 days (n=6-7 mice/group). (D) Bile acid amount and (E) gall bladder volume (F) plasma insulin (G) plasma glucose (H) plasma alanine aminotransferase (ALT) and (I) plasma aspartate aminotransferase (AST) in male Ad-control (Ad-Ctr) or Ad-*Zfp36l1* treated mice (n=10 mice/group). Gene expression analysis was determined by RT-qPCR and normalized to *Tbp*. All data shown as mean ± SEM. Asterisks indicate statistically significant differences (*p<0.05; **p<0.01; ***p<0.001) by Student's *t*-test.



Supplementary Figure 5 – ZFP36L1 loss-of-function alters bile acids *in vivo*
(A) Biliary bile acid amount (B) gall bladder volume (C) plasma triglyceride (TAG) (D) plasma free fatty acids (FFA) (E) plasma alanine aminotransferase (ALT) (F) plasma aspartate aminotransferase (AST) (G) plasma insulin and (H) plasma glucose in littermate male *Zfp36l1*$^{flox\text{-}flox}$ (n=10) and *Zfp36l1*$^{L\text{-}KO}$ mice (n=12). (I) VO_2, (J) VCO_2 (K) Activity of littermate male *Zfp36l1*$^{flox\text{-}flox}$ (n=5) and *Zfp36l1*$^{L\text{-}KO}$ mice (n=6) placed in metabolic cages at 60 days of age fed a standard rodent diet. All data shown as mean ± SEM. Asterisks indicate statistically significant differences (*p<0.05; **p<0.01) by Student's *t*-test for A-H and two way ANCOVA with repeated measures for I-K.



Supplementary Figure 6 – Loss of hepatic *Zfp36l1* results in resistance to diet-induced obesity, protection from steatosis and reduced lipid absorption.
(A) Lean mass in grams (g) of male littermate *Zfp36l1*$^{flox\text{-}flox}$ (n=31) and *Zfp36l1*$^{L\text{-}KO}$ (n=19) mice fed a Western diet for 64 days. (B) Body weight in grams (g) (C) fat mass in (g) and (D) lean mass in (g) of male littermate *Zfp36l1*$^{flox\text{-}flox}$ (n=6) and *Zfp36l1*$^{L\text{-}KO}$ (n=8) mice fed a high fat (HF; 45kCal) diet for 77 days (n=6-8 mice/genotype). (E) VO_2, (F) VCO_2 and (G) activity of male littermate *Zfp36l1*$^{flox\text{-}flox}$ (n=5) and *Zfp36l1*$^{L\text{-}KO}$ (n=6) mice fed a Western diet for 64 days. (H) Plasma glucose, (I) Plasma aspartate aminotransferase (AST) and (J) hepatic gene expression of *Il1b* and *Tnfa* in male littermate *Zfp36l1*$^{flox\text{-}flox}$ (n=12) and *Zfp36l1*$^{L\text{-}KO}$ (n=9) mice fed a Western diet for 64 days. (K) Fecal calorimetry analysis and (L) Fecal output of *Zfp36l1*$^{flox\text{-}flox}$ (n=12) and *Zfp36l1*$^{L\text{-}KO}$ (n=9) mice fed a Western diet for 64 days. All data shown as mean ± SEM. Asterisks indicate statistically significant differences (*p<0.05; **p<0.01) by two-way ANOVA with repeated measures for A-D, two-way ANCOVA with repeated measures for E-G and Student's *t*-test in H-L.

Fig. 3D

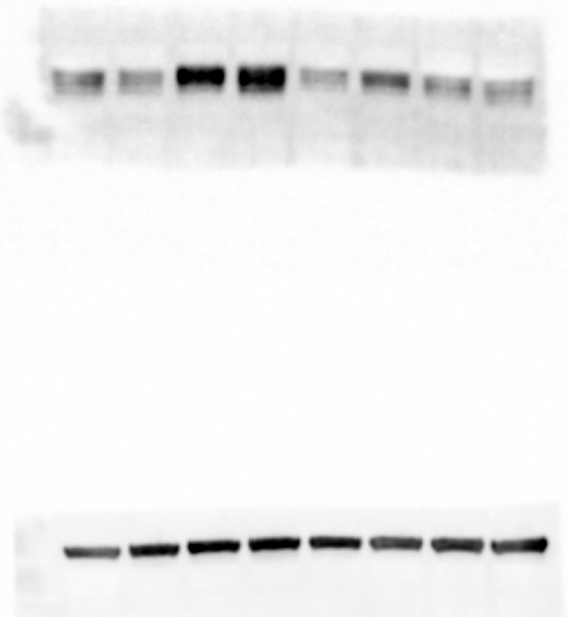


Fig. 3E

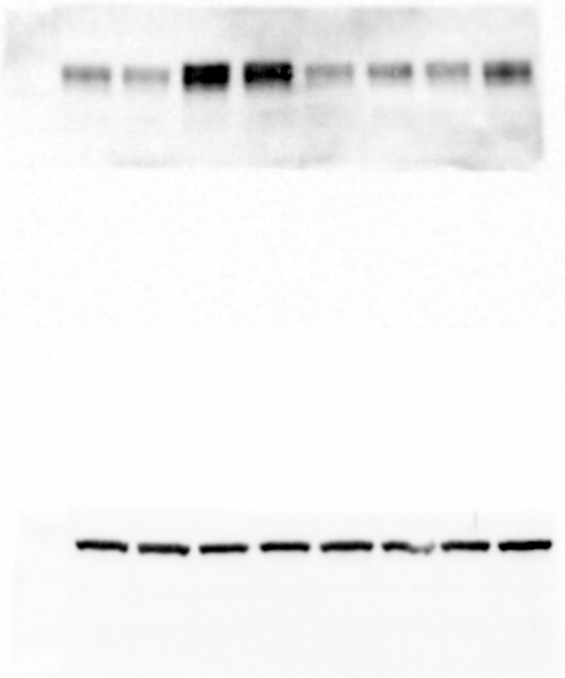
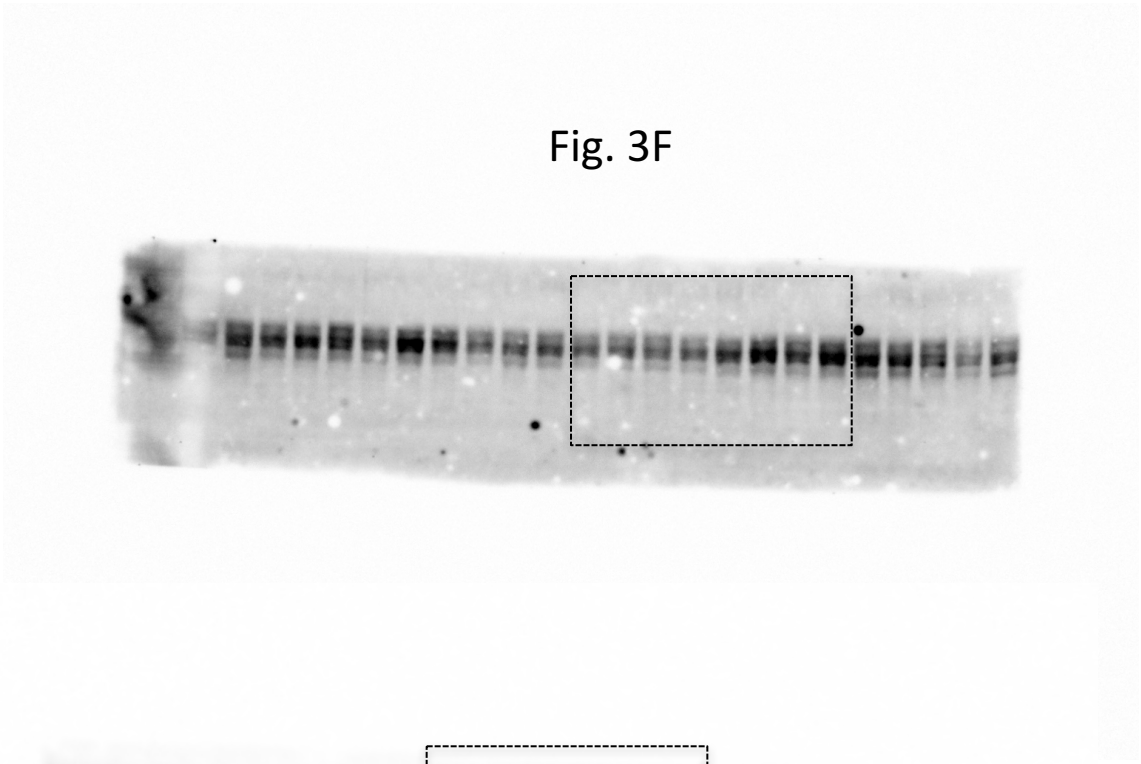


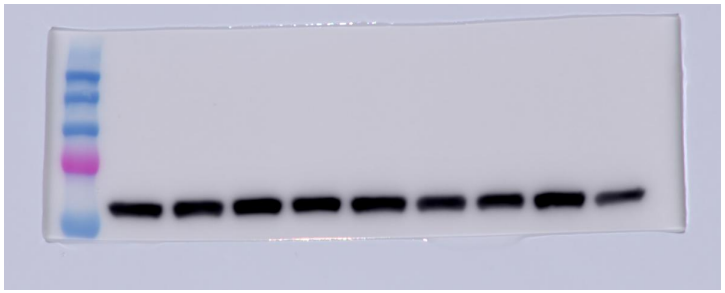
Fig. 3F



Supplementary Fig. 3C

ZFP36L1

PDI



Supplementary Fig. 4A

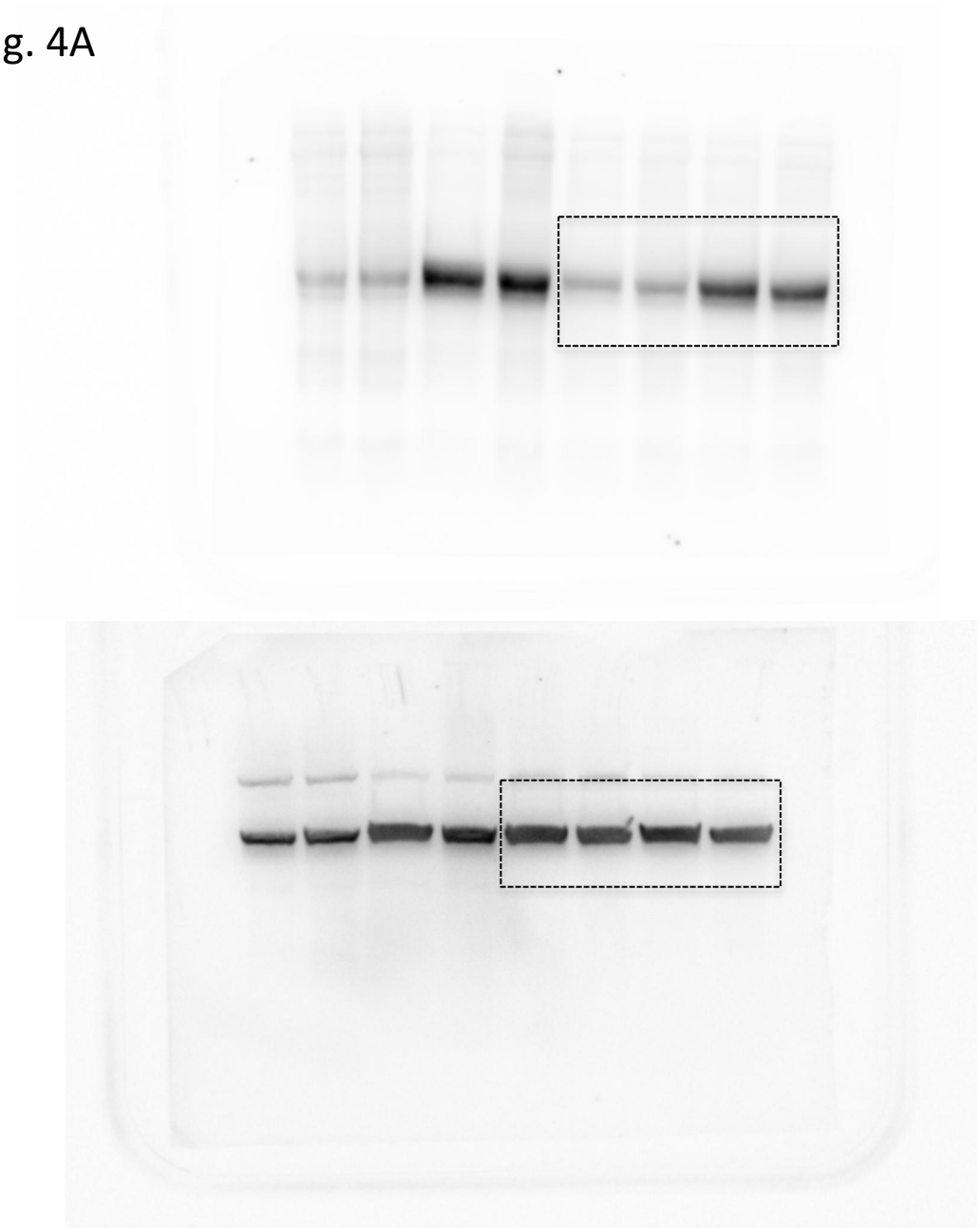
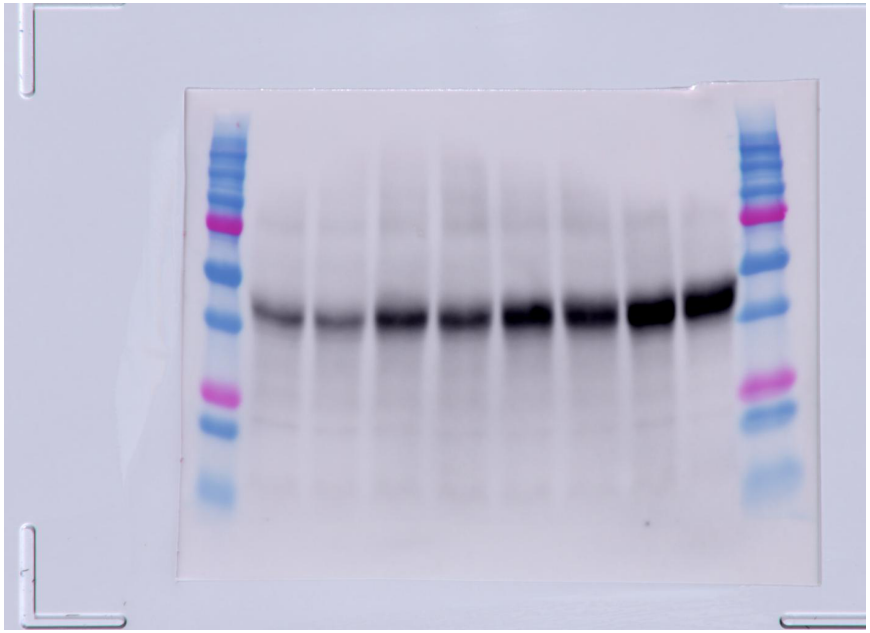


Fig. 4B

ZFP36L1



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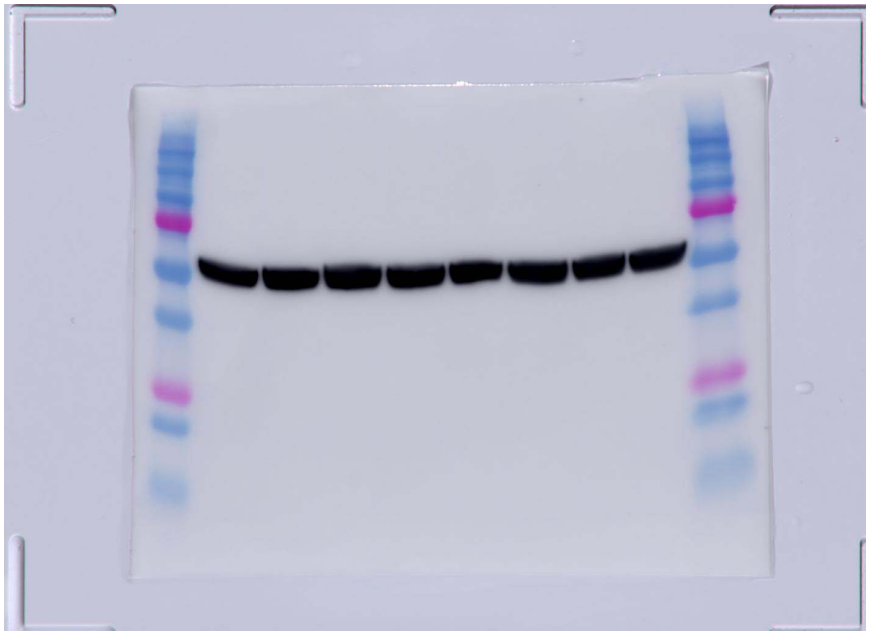
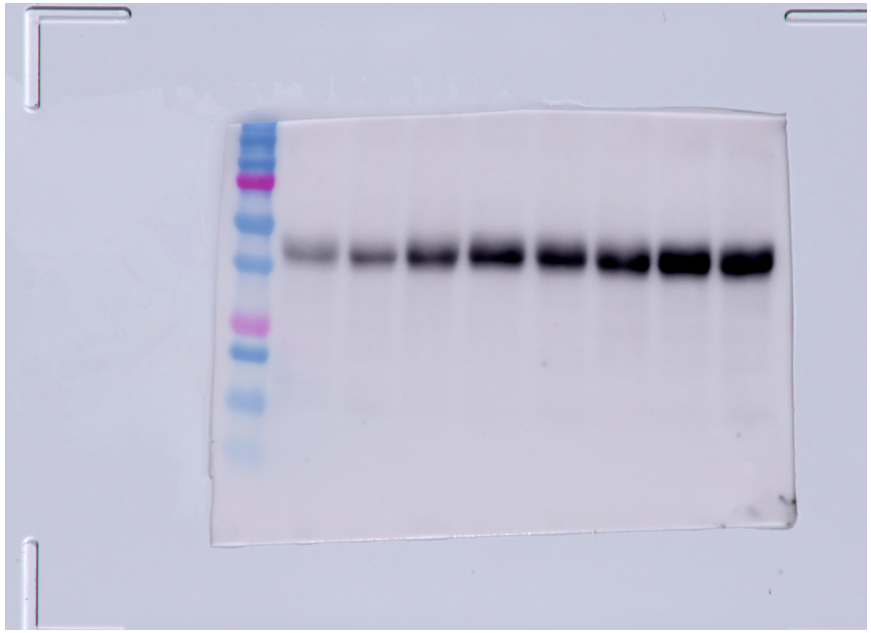


Fig. 4D

ZFP36L1



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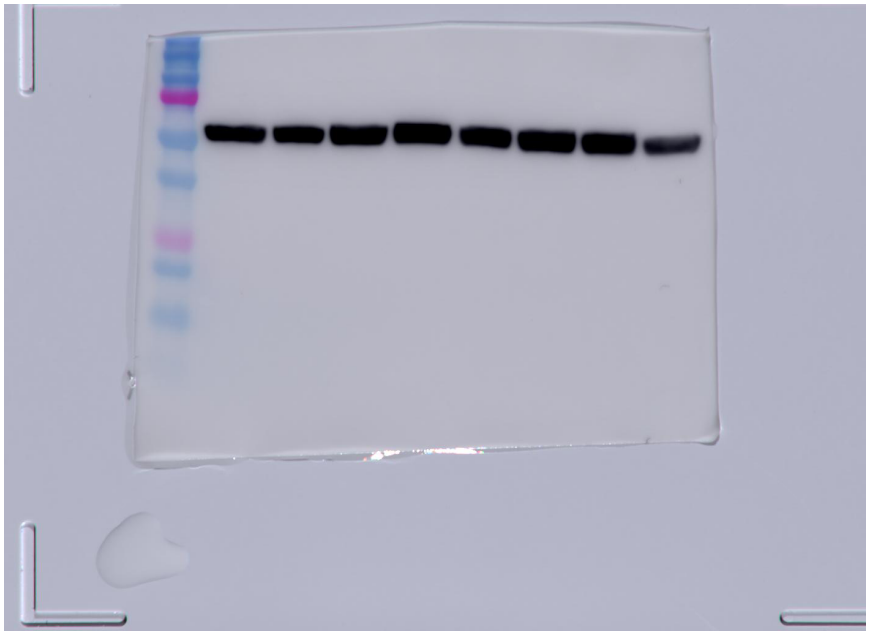
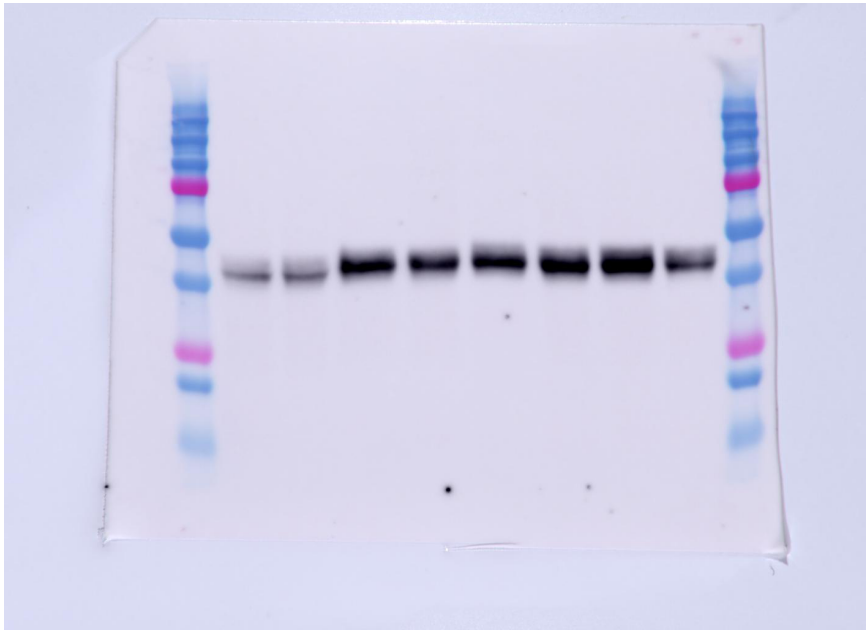


Fig. 4F

ZFP36L1



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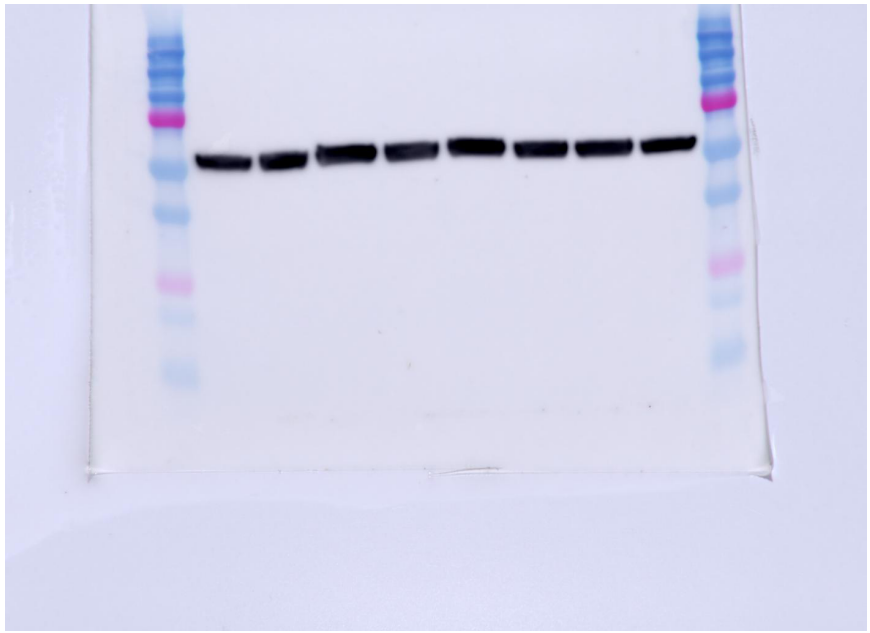
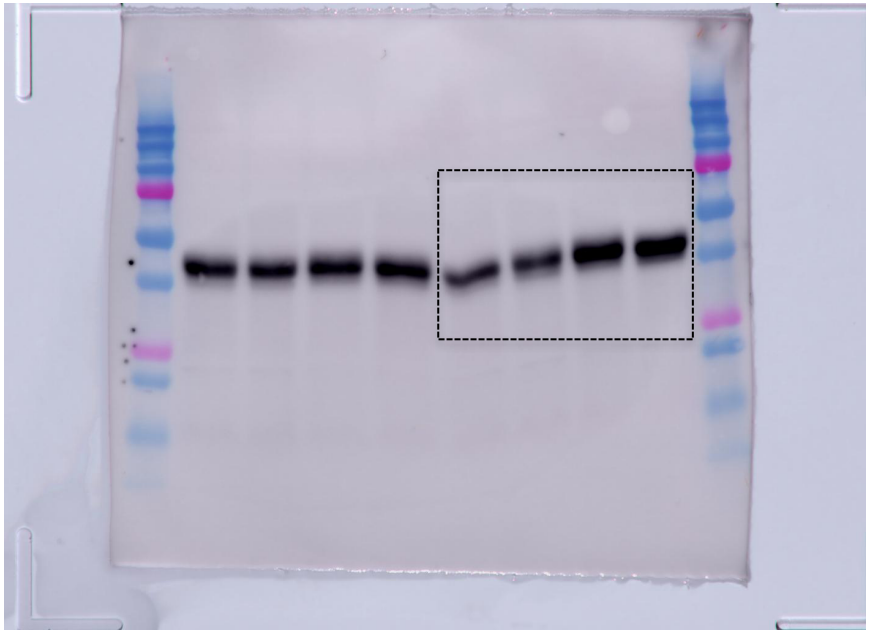


Fig. 5C

ZFP36L1



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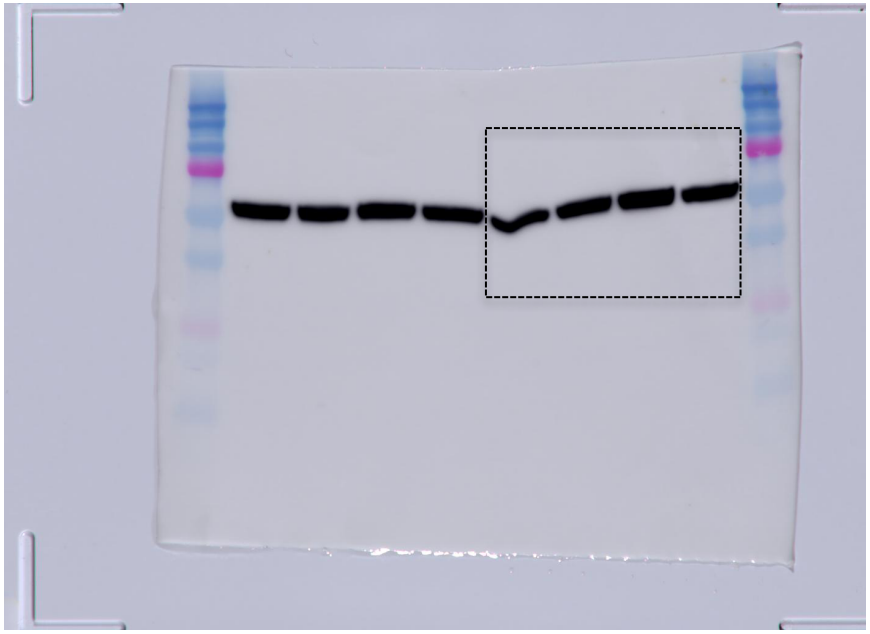
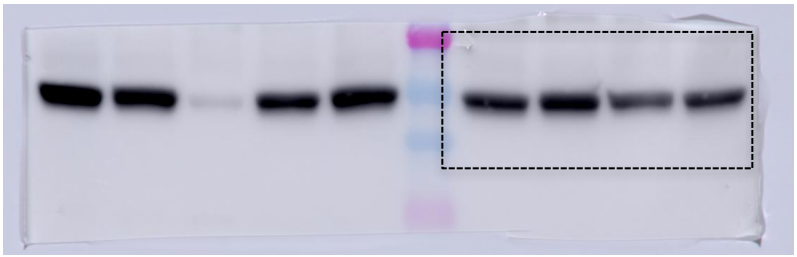


Fig. 5D

CYP7A1



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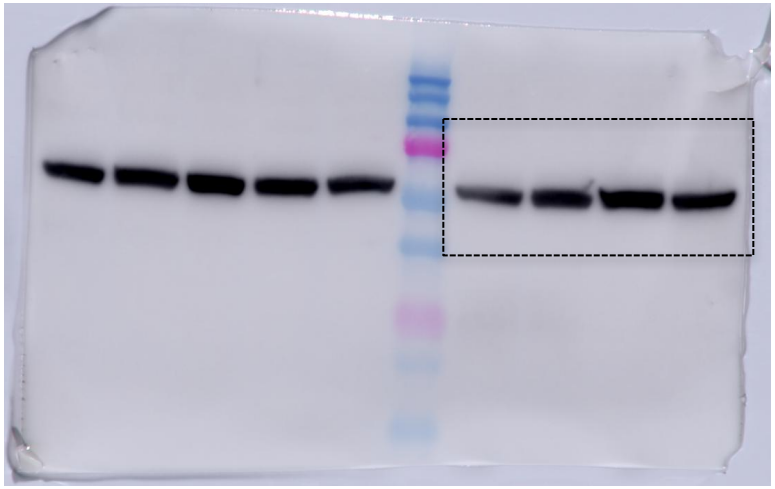
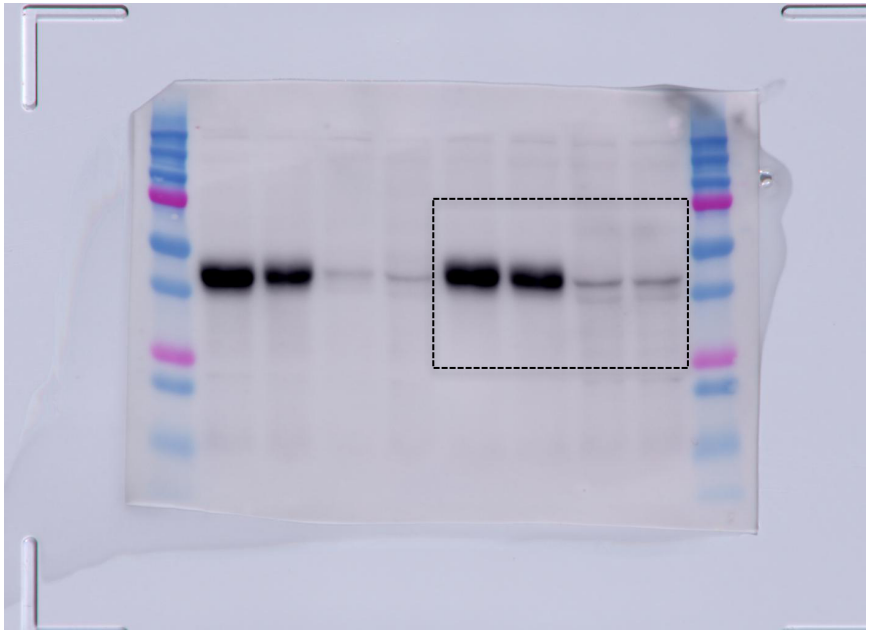


Fig. 6A

ZFP36L1



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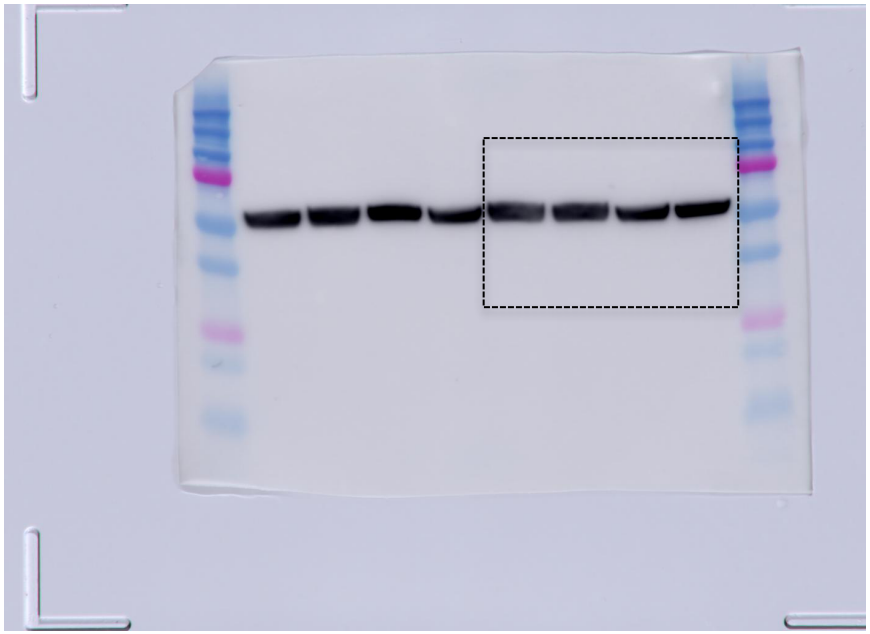
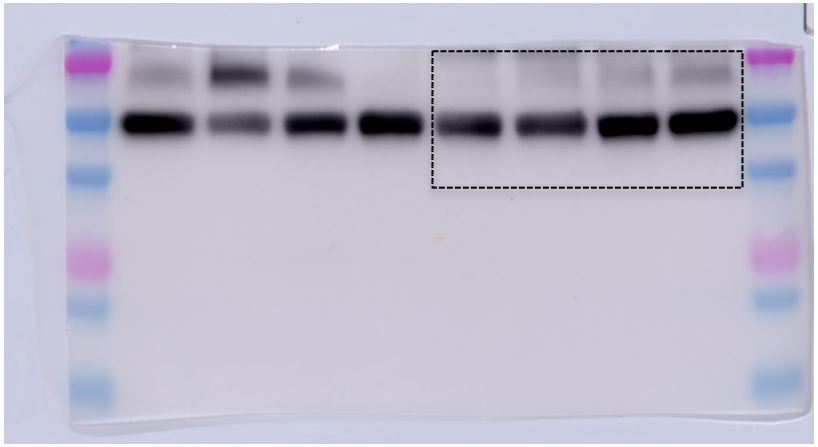


Fig. 6B

CYP7A1



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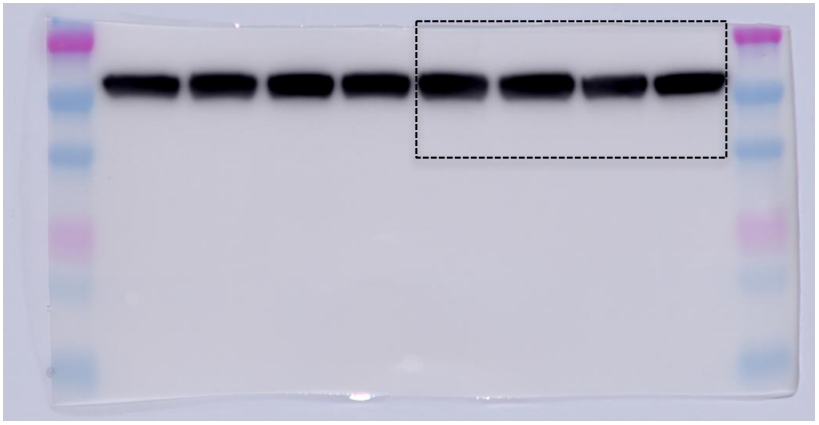

Fig. 8M