gene codes for HNF4α in human (Kritis AA et al., 1999), which is regulated by two different promoters. These promoters produce two isoform classes, P1 and P2 (Babeu JP et al., 2014). P1 isoforms are mainly expressed in the adult liver, whereas P2 isoforms have been detected in the liver during embryonic development and under pathological conditions such as cancer (Babeu JP et al., 2014; Walesky C et al., 2015; Tanaka T et al., 2006). The expression and function of HNF4α are regulated at multiple levels (Chellappa K et al., 2012; Guo H et al., 2014; Hong YH et al., 2003; Lu H et al., 2016, Song Y et al., 2015; Soutoglou E et al., 2000; Sun K et al., 2007; Xu Z et al., 2007; Yokoyama A et al., 2011; Zhou W et al., 2012).

Therefore, what is needed are compositions and methods for modulating HNF4α expression and/or treating liver diseases and/or liver disorders. The compositions and methods disclosed herein address these and other needs.

## SUMMARY

The compositions and methods disclosed herein address the certain unmet needs in liver disease treatment. In some ~~aspect~~examples, disclosed herein are compositions and uses thereof for a medicament for the treatment of liver diseases and/or liver disorders, wherein the composition increases an amount or function of one or more transcription factors selected from the group consisting of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and/or POM121C or decreases an amount or suppresses a function of one or more transcription factors selected from the group consisting of DNAJB1/HSP40, ATF6, ATF4, and PERK. In some ~~embodiment~~examples, the composition is a vector, and wherein the vector comprises one or more nucleic acids that encode the one or more of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and/or POM121C. In some ~~embodiment~~examples, the composition is a vector comprising a nucleic acid encoding HNF4α (e.g., HNF4α isoform 2). The compositions and the methods disclosed herein result in surprising increase in an amount of HNF4α in a hepatocyte (e.g., an increase in a total amount of HNF4α in the hepatocyte, and/or an increase in an amount of HNF4α in the nucleus of the hepatocyte), resulting in an effective treatment of liver diseases (e.g., an end-stage liver disease).

In some ~~aspect~~examples, disclosed herein is a method of treating a liver disease in a subject in need thereof comprising administering to the subject a composition, wherein the composition increases an amount or function of one or more transcription factors selected from the group consisting of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C.

In some ~~aspect~~examples, disclosed herein is a use of a composition for the preparation of a medicament for treatment a liver disease in a subject in need thereof comprising administering to the subject the composition, wherein the composition increases an amount or function of one or

more transcription factors selected from the group consisting of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C.

In one aspect, the present disclosure refers to use of a composition in the manufacture of a medicament for treating a liver disease in a subject in need thereof, wherein the composition increases an amount or function of one or more transcription factors selected from the group consisting of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C, and wherein the composition is a vector comprising a nucleic acid that encodes HNF4α isoform 2 (P1).

In some ~~embodiment~~examples, the composition is a vector, and wherein the vector comprises one or more nucleic acids that encode the one or more of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C. In some ~~embodiment~~examples, the vector comprises one or more nucleic acids that encode the PROX1 and/or SREBP1. The one or more nucleic acids can be a DNA or a mRNA.

In some ~~aspect~~examples, disclosed herein is a method of treating a liver disease in a subject in need thereof comprising administering to the subject a composition, wherein the composition decreases an amount or suppresses a function of one or more transcription factors selected from the group consisting of DNAJB1/HSP40, ATF6, ATF4, and PERK.

In some ~~aspect~~examples, disclosed herein is a use of a composition for the preparation of a medicament for treatment a liver disease in a subject in need thereof comprising administering to the subject the composition, wherein the composition decreases an amount or function of one or more transcription factors selected from the group consisting of DNAJB1/HSP40, ATF6, ATF4, and PERK.

In one aspect, the present disclosure refers to use of a composition in the manufacture of a medicament for treating a liver disease in a subject in need thereof, wherein the composition decreases an amount or suppresses a function of one or more transcription factors selected from the group consisting of DNAJB1/HSP40, ATF6, ATF4, and PERK.

In some ~~embodiment~~examples, the administration of the composition increases an amount of HNF4α in a nucleus of a hepatocyte in the subject. In some ~~embodiment~~examples, the administration of the composition does not increase a total amount of HNF4α in the hepatocyte. In some ~~embodiment~~examples, the administration of the composition increases a total amount of HNF4α in the hepatocyte.

In some ~~embodiment~~examples, the vector further comprises a nucleic acid that encodes HNF4α. In some ~~embodiment~~examples, the method further comprises administering to the subject a vector that comprises a nucleic acid that encodes HNF4α. In one example, the nucleic acid encodes HNF4α isoform 2.

In some ~~aspect~~examples, disclosed herein is a composition comprising a vector, wherein the vector comprises one or more nucleic acids that encode one or more transcription factors selected from the group consisting of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C, and functional fragments thereof.

In one aspect, the present disclosure refers to a composition comprising a vector, wherein the vector comprises one or more nucleic acids that encode HNF4α isoform 2 (P1) and one or more transcription factors selected from the group consisting of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C, and functional fragments thereof.

In some ~~aspect~~examples, disclosed herein is a method of treating a liver disease in a subject in need thereof comprising administering to the subject a vector that comprises a nucleic acid encoding HNF4α isoform 2.

In some ~~aspect~~examples, disclosed herein is a use of a vector for preparation for medicament for treatment of a liver disease, wherein the vector comprises a nucleic acid encoding HNF4α isoform 2.

In one aspect, the present disclosure refers to use of a vector that comprises nucleic acid that encodes HNF4α isoform 2 in the manufacture of a medicament for treating a liver disease in a subject in need thereof.

**DESCRIPTION OF DRAWINGS**

Figures 1A-1C show HNF4α location in hepatocytes from normal and cirrhotic livers. Figure 1A shows representative photographs of HNF4α immunofluorescence of isolated human hepatocytes from NASH decompensated liver and normal human hepatocytes. Western blot analysis and quantification of HNF4α normalized to Beta-Actin in hepatocytes isolated from functionally decompensated livers (NASH and alcohol-mediated Laennec's cirrhosis) (n=6) and hepatocytes isolated from normal liver controls (n=2). Figure 1A shows total HNF4α; normal human hepatocytes vs decompensated human hepatocytes, P = 0.166. Figure 1B shows cytoplasm HNF4α; normal human hepatocytes vs decompensated human hepatocytes, P = 0.023. Figure 1C shows nuclear HNF4α; normal human hepatocytes vs decompensated human hepatocytes, P = 0.023). Graphs from A to C are plotted as the mean ± SD. Statistically significant ($P < 0.05$). Diamonds show Child-Pugh “B” and squares show Child-Pugh “C”.

Figures 2A-2C show protein expression and Spearman’s rank correlation test of HNF4α post translational modifiers. Figures 2A and 2B show Western blot analysis (2A) and quantification (2B) of EGFR (P=0.904), cMET (P = 0.023), total AMPKα ($P > 0.999$), p-AMPKα(Thr172) (P=0.547), total AKT (P = 0.047), p-AKT(Ser473) (P = 0.547), p-AKT(Thr308) (P = 0.024), p-AMPKα(Thr172)/ AMPKα ratio (P=0.5476), p-AKT(Ser473) / AKT ratio (P=0.1667) and p-AKT(Thr308)/total AKT ratio (P = 0.0238) in decompensated NASH (n=4) and alcohol-mediated Laennec's cirrhotic hepatocytes (n=2) and normal control hepatocytes (n=2). In Fig. 2B, filled squares refer to Child-Pugh “B” and filled diamonds refer to Child-Pugh “C”. Figure 2C shows that Spearman’s rank correlation test is shown and demonstrates that nuclear HNF4α correlates significantly with cMET (r = 0.71; P = 0.037), total AKT (r = 0.71; P = 0.037), phospho-AKT(Thr308) (r = 0.82; P = 0.011), and phospho-AKT(Thr308)/total AKT ratio (r = 0.73; P = 0.031). Cytoplasmic HNF4α showed significant correlation with cMET (r = -0.80; P = 0.014), total AKT (r = -0.73; P = 0.031), phospho-AKT(Thr308) (r = -0.77; P =0.021, and phospho-AKT(Thr308)/total AKT ratio (r = - 0.72; P = 0.037). Bar graphs of Figure 2B are plotted as the mean ± SD. Statistically significant ($P < 0.05$).

## CLAIMS

What is claimed is:

1. ~~A method of treating a liver disease in a subject in need thereof comprising administering to the subject~~Use of a composition in the manufacture of a medicament for treating a liver disease in a subject in need thereof, wherein the composition increases an amount or function of one or more transcription factors selected from the group consisting of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C, and wherein the composition is a vector comprising a nucleic acid that encodes HNF4α isoform 2 (P1).

2. The use~~method~~ of claim 1, ~~wherein the composition is a vector, and~~ wherein the vector further comprises one or more nucleic acids that encode the one or more of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C.

3. The use~~method~~ of claim 1, ~~wherein the composition is a vector, and~~ wherein the vector further comprises one or more nucleic acids that encode the PROX1 and/or SREBP1.

4. The use~~method~~ of any one of claims 1-3, wherein the one or more nucleic acids are a DNA or a mRNA.

5. The use~~method~~ of any one of claims 1-4, wherein the administration of the composition increases an amount of HNF4α in a nucleus of a hepatocyte in the subject.

6. The use~~method~~ of any one of claims 1-5, wherein the administration of the composition does not increase a total amount of HNF4α in the hepatocyte.

7. The use~~method~~ of any one of claims 1-6, wherein the administration of the composition increases a total amount of HNF4α in the hepatocyte.

8. ~~The method of any one of claims 1-7, wherein the vector further comprises a nucleic acid that encodes HNF4α.~~

~~9. The method of any one of claims 1-7, further comprising administering to the subject a vector that comprises a nucleic acid that encodes HNF4α.~~

~~10. The method of claim 8 or 9, wherein the nucleic acid encodes HNF4α isoform 2 (P1).~~

~~11.~~8. The use~~method~~ of claim ~~8 or 9~~1, wherein the nucleic acid that encodes HNF4α comprises SEQ ID NO:1.

~~12.~~9. The use~~method~~ of any one of claims 1-~~11~~8, wherein the liver disease is liver fibrosis, liver cirrhosis, liver cancer, or end-stage liver disease.

~~13.~~10. The use~~method~~ of any one of claims 1-~~12~~9, wherein the liver disease is liver cirrhosis.

~~14.~~11. The use~~method~~ of any one of claims 1-~~13~~10, wherein the subject is a human.

~~15.~~12. ~~A method of treating a liver disease in a subject in need thereof comprising administering to the subject~~Use of a composition in the manufacture of a medicament for treating a liver disease in a subject in need thereof, wherein the composition decreases an amount or suppresses a function of one or more transcription factors selected from the group consisting of DNAJB1/HSP40, ATF6, ATF4, and PERK.

~~16.~~13. The use~~method~~ of claim ~~15~~12, wherein the composition is a nucleic acid.

~~17.~~14. The use~~method~~ of claim ~~16~~13, wherein the nucleic acid is a DNA or a RNA.

~~18.~~15. The use~~method~~ of any one of claims ~~15-17~~12-14, wherein the administration of the nucleic acid increases an amount of HNF4α in a nucleus of a hepatocyte in the subject.

~~19.~~16. The use~~method~~ of any one of claims ~~15-18~~12-15, wherein the administration of the composition does not increase a total amount of HNF4α in the hepatocyte.

~~20.~~17. The use~~method~~ of any one of claims ~~15-19~~12-16, wherein the administration of the composition increases a total amount of HNF4α in the hepatocyte.

~~21.~~18. The use~~method~~ of any one of claims ~~15-20~~12-17, wherein the composition further comprises a nucleic acid that encodes HNF4α.

~~22.~~19. The use~~method~~ of any one of claims ~~15-21~~12-18, wherein ~~further comprising administering to the subject~~ a vector that comprises a nucleic acid that encodes HNF4α is to be further administered to the subject.

~~23.~~20. The use~~method~~ of claim ~~21-~~18 or ~~22~~19, wherein the nucleic acid encodes HNF4α isoform 2.

~~24.~~21. The use~~method~~ of claim ~~21-~~18 or ~~22~~19, wherein the nucleic acid that encodes HNF4α comprises SEQ ID NO:1.

~~25.~~22. The use~~method~~ of any one of claims ~~15-24~~12-21, wherein the liver disease comprises liver fibrosis, liver cirrhosis, liver cancer, or an end-stage liver disease.

~~26.~~23. The use~~method~~ of any one of claims ~~15-25~~12-22, wherein the subject is a human.

~~27.~~24. A composition comprising a vector, wherein the vector comprises one or more nucleic acids that encode HNF4α isoform 2 (P1) and one or more transcription factors selected from the group consisting of PROX1, NR5A2, NR0B2, MTF1, SREBP1, EP300, and POM121C, and functional fragments thereof.

~~28. The composition of claim 27, further comprising another vector comprising a nucleic acid that encodes HNF4α.~~

~~29.~~25. The composition of claim ~~28~~24, wherein the nucleic acid that encodes HNF4α isoform 2 (P1) comprises SEQ ID NO:1.

~~30.~~26. ~~A method of treating a liver disease in a subject in need thereof comprising administering to the subject~~Use of a vector that comprises nucleic acid that encodes HNF4α isoform 2 in the manufacture of a medicament for treating a liver disease in a subject in need thereof.

~~31.~~27. The use~~method~~ of claim ~~30~~26, wherein the nucleic acid comprises SEQ ID NO:1.

~~32.~~28. The use~~method~~ of claim ~~30~~ 26 or ~~31~~27, wherein the liver disease is liver fibrosis, liver cirrhosis, liver cancer, or an end-stage liver disease.

~~33.~~29. The use~~method~~ of claim ~~32~~28, wherein the liver disease is liver cirrhosis.

~~34.~~30. The use~~method~~ of any one of claims ~~30~~26-~~33~~29, wherein the subject is a human.